The Oxford Medicine

BY VARIOUS AUTHORS

VOLUME I

EDITED BY

HENRY A. CHRISTIAN A.M. M.D. LL.D. Sc.D. (Hon.) M.A.C.P.
Hon. F.R.C.P. (Can.) D.S.M. (A.M.A.)

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Sometime Clinical Professor of Medicine Tufts College Medical School
Sometime Visiting Physician Beth Israel Hospital
Physician in Chief Emeritus Peter Bent Brigham Hospital Boston Mass

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TO MY WIFE

ELIZABETH SEARS CHRISTIAN

WHO WITH WONDERFUL LOVE AND UNDERSTANDING HAS CREATED AN ATMOSPHERE OF PERFECT HOME LIFE IN WHICH HAPPILY I HAVE WORKED THESE VOLUMES ARE DEDICATED BY THEIR EDITOR

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PREFACE

At the time of the planning of these volumes in 1918 medicine was undergoing rapid and far reaching changes. A functional concept of medicine to a considerable extent had supplemented the older structural concept. This brought into use many new methods of studying patients, and from these much new data had been accumulated, correlated and interpreted in relation to disease. Physicians in America and England were active in this work and as a result they contributed much to these newer developments. A number of years had elapsed since a system of medicine in English had been published, and this seemed an opportune time to issue a system of medicine by American and English physicians in which their viewpoints were to be presented.

Newer publishing methods made it possible to issue in parts, to supplement at will and to replace from time to time as views change. Under these conditions a medicine written for the present can be maintained in tune with succeeding periods and need not lose its value, since it will not get out of date. Such a method has been used in this work in all the succeeding years.

Editorial supervision by the present editor has continued since the inauguration of this system of medicine. For the first few years he had the assistance of Sir James Mackenzie; then it became entirely a one man job editorially and so continued until the present time (1949); recently three co-editors have been invited to join in the editorial work.

Representative American and English men of medicine have contributed. Emphasis throughout has been placed on function. Structure, however, has not been neglected, but when possible, it has been interpreted in terms of function. Treatment has received adequate discussion. A simplified statement of methods of treatment in relation to function has been needed. Treatment is perhaps the most difficult part of medicine to deal with, because so much of it remains empirical and inexact. Still we do treat our patients with much benefit to them, and it should be possible to describe the methods advised in such a way that the reader may carry them out for himself. Such an attempt has been made in these volumes.

January 1, 1949

Henry A. Christian
Editor

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INTRODUCTION

I

PRESENT DAY MEDICINE

By HENRY A CHRISTIAN

Medicine like other sciences advances by a periodic progression for a certain time a method or a viewpoint dominates and the investigations and consequent progress are apt to be along the same general lines Then comes a new method of study to change the aspect of medicine and a new period is inaugurated The length of the period varies in relation to the dominance of a method and its productivity With different periods of development we associate certain names of men but methods and viewpoint rather than men determine periods in the history of medicine names persist because the strong minds of a period dominate as they develop and apply the methods or interpret their results to their colleagues Names loom large in retrospection rather than at the time Perspective often is needed to rate properly the men of a period names currently prominent too frequently pass into oblivion when it is realized that their part after all has been but interpretation and application while others have been the contributors of the new to the period and a rare man has been the creative genius whose work largely has instigated the investigations and the methods characteristic of the period

Virchow s name stands out from the middle of the nineteenth century as the prominent one of a period in medicine which may be termed a period of the dominance of a structural pathology In the last quarter of the same century a new period in medicine was inaugurated by the invaluable investigations of Pasteur Lister and Koch a bacteriological or etiological period During both these periods in clinical medicine as is pointed out in the next part by Sir James Mackenzie physical signs have been the center of interest as the expression during life of a structural pathology and as the result of causative agents The physician has busied himself chiefly in the greater part of the nineteenth century with the discovery and the elucidation of physical signs of disease with

methods of investigating and recording them in ways bringing them into the ken of our special senses and with the effort by therapeutic measures to influence physical signs as an index of a change in the diseased condition

In a similar sense to that which has led us to speak of the third quarter of the nineteenth century as a period of dominance in medicine of a structural pathology the present may be designated as a period of physiological (including biochemical) or functional dominance which had its beginning in the early days of the twentieth century and is now in full swing Today our interest is more in what an organ or a group of organs can do as an effect of the changed conditions of disease and in how the body activity as a whole may be influenced by the general or local effects of abnormal conditions than it is in structure Structure still is important for in last analysis no adequate understanding of dis ease can come until a correlation between structure and function can be made Today, however advances seem to be made more along the lines of study of function than of structure

Unfortunately in this very fact lies a danger It is but natural to turn toward those methods of study which seem most productive of advance and to concentrate on them to the neglect of other knowledge whose significance is none the less great in the final understanding of the whole Already we see the evil result of this in the new generations of medical men quite ignorant of many of the facts of pathological anatomy which are fundamental to an understanding of disease its recognition and its treatment We find pathological physiologists and bacteriologists as well as clinicians whose interpretation of observations falls into error by reason of a lack of proper fundamental training and knowledge of the methods of pathological anatomy Both teachers and practitioners of medicine need to keep this in mind and to guard against the fault of neglect of pathological anatomy and its structural concept

One effect of present day interest in the utilization of physiological and chemical methods in the study of disease seems to have been a tendency to minimize the value of pathological observation with a conse quent decrease in the number of post mortem examinations The percentage of autopsies made on our fatal cases at least in America is decreasing This is most unfortunate for medicine Even if we grant as some would claim that little further advance in medicine is to be expected from post mortem study—a claim which in my judgment is not true—still thorough examination after death remains the most valuable check which we possess as to the correctness of the results of our ante mortem studies of patients and for this reason alone if nothing

else was to be contributed every effort should be made to obtain permission for a post mortem examination of the body of every patient that dies That physician who continues to practice medicine and never submits his theories of disease and his diagnosis to the test of a careful inspection of the end result of disease fails to secure for himself the most valuable check against fanciful theory and absolute misconception Without it he acquires a dangerous facility in misdiagnosis and a self satisfaction in his methods that early become fatal to his progress The autopsy which reveals to the physician or surgeon his error in diagnosis and treatment stimulates to renewed effort to improve the quality of his work His next case is examined more thoroughly is thought over more carefully and receives a better treatment by reason of his having had demonstrated to him his previous mistake in deduction and conclusion It is a poor physician indeed that does not learn something of value from each autopsy and this is just as true today as it was in the period of dominance of pathological anatomy in medicine

Many explanations have been sought for the distressingly small number of autopsies obtained at the present time Undoubtedly many factors contribute but I feel sure a large part of the blame lies at the door of the physician himself In a hospital the chief of service fails to appear at the time of the autopsy His neglect to come tends to create in the juniors the feeling that the autopsy after all is relatively unimportant and they grow less keen to obtain the necessary permission for autopsy Failure to attend is not due solely to carelessness or to having no time available Too often the chief-of service of today knows too little about what he sees at autopsy to appreciate fully its value or learn its lesson for his training has been physiological or chemical to the neglect of pathology and some do not care to expose their ignorance of pathological anatomy In hospitals where the visiting staff attends and understands the autopsies the percentage of autopsies is much larger Chiefs of staffs and hospital attendants would do well to ponder their own figures for autopsies and search themselves for a cause of the poor showing if such there be

In private practice the autopsy has become wellnigh obsolete The difficulties here are greater we grant However if we turn to the great names of the past we find that our predecessors found means for post mortem examination in private work Many made their own examinations and became quite excellent pathologists This custom should be revived Particularly does its revival become important if Sir James Mackenzie s ideas as to the future advances of medicine come true advances to be made by the careful observation of the general practitioner to whom come the beginnings of disease when structural changes

methods of investigating and recording them in ways bringing them into the ken of our special senses and with the effort by therapeutic measures to influence physical signs as an index of a change in the diseased condition

In a similar sense to that which has led us to speak of the third quarter of the nineteenth century as a period of dominance in medicine of a structural pathology the present may be designated as a period of physiological (including biochemical) or functional dominance which had its beginning in the early days of the twentieth century and is now in full swing Today our interest is more in what an organ or a group of organs can do as an effect of the changed conditions of disease and in how the body activity as a whole may be influenced by the general or local effects of abnormal conditions than it is in structure Structure still is important for in last analysis no adequate understanding of disease can come until a correlation between structure and function can be made Today however advances seem to be made more along the lines of study of function than of structure

Unfortunately in this very fact lies a danger It is but natural to turn toward those methods of study which seem most productive of advance and to concentrate on them to the neglect of other knowledge whose significance is none the less great in the final understanding of the whole Already we see the evil result of this in the new generations of medical men quite ignorant of many of the facts of pathological anatomy which are fundamental to an understanding of disease its recognition and its treatment We find pathological physiologists and bacteriologists as well as clinicians whose interpretation of observations falls into error by reason of a lack of proper fundamental training and knowledge of the methods of pathological anatomy Both teachers and practitioners of medicine need to keep this in mind and to guard against the fault of neglect of pathological anatomy and its structural concept

One effect of present day interest in the utilization of physiological and chemical methods in the study of disease seems to have been a tendency to minimize the value of pathological observation with a consequent decrease in the number of post mortem examinations The percentage of autopsies made on our fatal cases at least in America is decreasing This is most unfortunate for medicine Even if we grant as some would claim that little further advance in medicine is to be expected from post mortem study—a claim which in my judgment is not true—still thorough examination after death remains the most valuable check which we possess as to the correctness of the results of our ante mortem studies of patients and for this reason alone if nothing

nizing and recording variations in function whether they could be correlated with structural changes or not

During these same years remarkable developments were taking place in chemistry Both analytic and synthetic chemical methods rapidly were being applied to the study of organic substances With increasing knowledge of organic chemistry the chemists turned to the problem of the chemical constitution of living matter While as yet relatively little is known of the actual chemical structure of living matter great progress has been made in our knowledge of biochemistry From the chemists have come many methods applicable to the study in man of the products of body or organ activity These have yielded new data expressive of the function of tissues and as with physiological methods have often recorded evidences of change where no structural change could be made out

Very lately important extensions of knowledge have been made with the methods of physical chemistry and these applied to the living organism have furnished us with more information in regard to the mechanism of body activity The laws of physical chemistry are very important in an understanding of the equilibrium of body fluids which seems so necessary for life itself Slight changes in tissue fluids such as are to be detected by the methods of physical chemistry frequently are the index of variations in body function where other means fail to show a change and where no structural variation can be detected

From the bacteriologist the physiologist and the chemist (both biochemist and physical chemist) the clinician obtained methods these methods he has improved in their applicability to man and with them has observed and recorded changes until he has accumulated a vast store of data in regard to function Methods of study of function have come to have a place of dominance and from them has been built up a functional concept of disease which at the present time plays a very large part in medicine Functional methods give many new means of approach to diagnosis and they are now included of course among the ways taught to the student of recognizing diseased processes

The functional concept of today has had a very large effect on the treatment of disease The structural viewpoint of the pathological anatomists of the last century tended toward skepticism as to the possibility of improving conditions by treatment It was natural for the physician who appreciated the anatomical changes in such processes as the cirrhotic liver or tuberculous lung to feel that the damage done was irreparable and that the destroyed cells could not be regenerated For many of these not unnaturally there developed a veritable nihilism toward therapeutics

cannot be detected and whose opportunity it is to study disease from inception to ending. How important it is for that type of clinician to follow his problem to its finish and after death to observe the final effect of what for years he has been watching as little by little it grew from the stage of symptoms alone to that of physical signs from the stage of little interference with activity to the stage of bedridden disability and on to the culmination in death!

In this question of post mortem examination and a knowledge by the clinician of pathological anatomy the medicine of today has taken a backward step. Pathology plays as large a part as ever in medicine only it is not the sole or chief part. Function rather than structure is our chief interest today and yet function is in large measure dependent on structure and to be understood thoroughly anatomical changes need to be known. For this pathological anatomy is needed as before, only now it is not the final stage of the knowledge that we seek it is rather one of several means to a larger understanding of medicine.

That our interest has turned more and more toward function is not unnatural. After all it is what the body can do rather than how the organs look which concerns both patient and physician. Even with the utmost refinements of the technique of the present the highest powers of the microscope sometimes fail to reveal evidences of structural change in patients where during life there was every evidence of disorder. These negative findings at autopsy have stimulated investigators to utilize other methods of studying disease. A search for causes has developed other methods of observation than the microscope. The discovery of ultra microscopic or non filterable organisms for example has necessitated other means of examination than those depending on any form of visibility. These organisms are recognized and classified by their effects really a functional method.

In the progress of physiology much apparatus was devised to record the function of animal tissues to seek to apply these in the clinic became the almost obvious thing for the clinician. The clinician's attempts stimulated the effort to create better means of recording and apparatus more suitable to use on man. Soon as the result of the use of this apparatus, a large body of data became available for correlation and interpretation. Some of this was of a nature that reasonably could be harmonized with what might be expected as the effect of changes in structure and as anticipated these changes in structure subsequently were found. In many instances however by applying these physiological methods changes in function were observed to take place and yet careful search failed to show any corresponding change in structure. These things stimulated interest in function and in methods for recog

nizing and recording variations in function whether they could be correlated with structural changes or not

During these same years remarkable developments were taking place in chemistry Both analytic and synthetic chemical methods rapidly were being applied to the study of organic substances With increasing knowledge of organic chemistry the chemists turned to the problem of the chemical constitution of living matter While as yet relatively little is known of the actual chemical structure of living matter great progress has been made in our knowledge of biochemistry From the chemists have come many methods applicable to the study in man of the products of body or organ activity These have yielded new data expressive of the function of tissues and as with physiological methods have often recorded evidences of change where no structural change could be made out

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In contrast to them the physician of today with means of determining by test the functional efficiency of an organ has learned that often the organ which shows extensive anatomical change does its required work efficiently Moreover besides a large factor of safety in function of single organs they have learned that under the stimulus of need other tissues may take on the work of the damaged one The correlative activities of organs have become of great importance in both an understanding of body activities and an appreciation of ways and means of influencing body function

Animal experimentation has shown the very great extent of repair and regeneration that is possible after injury of cellular organs In fact the extreme power of repair in their tissues makes it very difficult to produce in animals chronic changes such as we see in man in the later stages of disease Presumably human tissues too have great powers to regenerate only in man we have little opportunity to study them anatomically in these stages Functional study however indicates that extensive reparative processes are possible

The effects of fatigue and the improvement from rest which we know to occur do not show themselves in structure Tests of function give us a measure of these fatigue changes whether they result from overuse or are caused by ordinary use of an organ impaired by disease In recent years our knowledge has been increased greatly in respect to many kinds of depressed and deranged function where we find no parallel structural change

The factor of safety in tissues the power of repair and regeneration and the effects of fatigue and rest are portions of the functional concept of today which change our views as to treatment and give us a different opinion as to the possibility of improvement when adequate measures are applied to the body Instead of therapeutic nihilism there is the expectancy of good results from properly conceived and adequately carried out forms of therapeutics in the sense that function is improved even though the anatomical change produced by the disease is permanent

Another cause has been operative too in influencing our methods of treating disease Investigations in parasitology and bacteriology have yielded much information as to the ways in which organisms act on the body tissues and how these tissues react to the organisms From such studies have come the protective inoculations against disease on the principle of increasing body resistance in a specific way and the curative sera whether antitoxic or antibacterial A better understanding of non specific tissue resistance also has been obtained and these principles are used in managing infectious diseases

Of the very greatest importance are the advances which have been

made in specific chemotherapy Workers skilled in chemistry have made synthetically long series of substances closely allied in structural formula and the action of these has been tested on pathogenic organisms in animals until one has been found which combines the properties of maximal injurious action on the pathogenic organism with minimal deleterious effect on the tissues of the host In this way we have been supplied with drugs capable of the most marked effect on diseases produced by parasites

For these various reasons much change has been brought about in the present-day therapeutics whether the agent used is drug serum diet or physical method Treatment has become more rational Of course much of our knowledge of treatment remains empirical but even purely empirical methods are capable of being tested by means of studying function and though we may not know the how still we can feel sure that a given means will influence function in a given direction and so be indicated under certain conditions

At present we are in a position to make pretty definite statements in regard to the treatment of many conditions Our knowledge justifies us in eliminating some of the methods of the past and replacing them by better Some drugs now discarded may find new uses in the future when more is learned in regard to them It is to be expected that treatment will remain a changing subject about which the final word for any disease rarely can be given Still it is possible to outline a simplified method of management for many diseased conditions a management which in the broad sense is treatment or therapeutics This should be an important part of a new medicine based on our present knowledge

In the training of the medical man to provide him with a proper knowledge of the relationship between function and structure there is needed a balance between the fundamental or basal parts of medicine (anatomy physiology biochemistry pathology bacteriology and pharmacology) and their practical applications to man which constitute the practice of medicine There is an optimum balance to be sought in such applications between general medicine and the specialties and between the laboratory and the clinic First the fundamental parts need to be studied by themselves then the student must be instructed in the methods of examining patients Next should come drill and practice in methods on the sick man in varying stages of disease with observation as to the results of methods of treatment It is most important in acquiring a conception of disease to get a proper integration between these two more or less separable parts of the beginnings of a medical education Ordinarily this requires some return to the fundamental branches after their application has been practiced for a time in the clinic or in general

practice. Obviously specialization should come relatively late in development, but the specialties are no immediate concern of this discussion of present day medicine.

Finally, the man ready to practice modern medicine needs to possess a proper balance between so-called laboratory methods and those of history taking and simple observation. In the immediate past there has been a distinct tendency to overvalue the laboratory and to undervalue the means that made of our predecessors very sound practitioners of the medicine of their day. In respect to these two phases of medicine a changing balance is needed and the medical man must remain versed in both. This balance would seem to be maintained best by an organization of the clinic so that each worker spends part of his time in the clinic and part in the laboratory, finding his problems in the former and aiding their solution by means and methods in the latter. Too continued isolation in either the laboratory or the clinic is bad for the man who is to be a leader in medicine. Neglect of the methods of either would be equally harmful.

In private practice just the same balances need to be maintained. In fact the medicine of today for the practitioner is dependent upon the power to utilize information about his patients obtained from both laboratory and direct observation. In both some of the work almost necessarily must be done for the practitioner, but the final interpretation of the data has to be made by the single individual, the clinician. Complex methods, especially those yielding numerical values, often have an apparent accuracy which may be very misleading. It is highly important to keep this in mind so as not to be tempted to neglect the old-fashioned and simple methods of observation of the patient in connection with his story of his symptoms and their development.

Diagnosis in final analysis depends on proper evaluation of symptoms and signs, recorded by all available means and interpreted with the critical judgment of a large common sense. It needs to be recognized that symptoms antedate signs, and that the beginnings of disease may be present and productive of symptoms when no available method can detect abnormality in structure, and even tests of function record no change. Treatment to be successful must depend on a correct diagnosis. For a diagnosis often many methods of study must be applied to the patient. Methods of treatment always must be properly adjusted to the individual idiosyncrasy of the patient. Continued observation of the most careful sort is needed to estimate the effects of treatment. All of this is required by the man who is to become a good practitioner of medicine. Common sense and judgment cannot be replaced safely by graphic methods of recording, and yet many mechanical methods are

of the greatest value when properly used and interpreted The medicine of today furnishes us with many ways of studying our patients some new many old some to detect structural changes others to measure disturbances in function For some patients few methods need to be used for others many ways of examining must be employed Experience and critical judgment serve as guides to the necessary procedure in the individual patient

To the man who works either in the hospital or in the family the opportunity offered by the medicine of today is great Much is known much remains to be discovered Both the beginnings and endings of diseased processes contain much as yet unexplored Present-day methods of studying *function and structure furnish to all the means of being investigators In both private practice and in institutions observations* may be made which as they accumulate necessarily must throw light in dark places He who is in medicine both to advance our knowledge and to alleviate suffering in the individual remains as always the ideal physician

I

THE FUTURE OF MEDICINE

By SIR JAMES MACKENZIE

A NEW work on medicine which has been compiled by authorities on the different diseases may be taken as representative of the state of medical knowledge at the time of issue The occasion may be taken to consider the stage which medical progress has reached in order to find out if the advance is being made along those lines likely to achieve the best results This will be found necessary if we reflect upon the history of medicine The aim of all interested in the investigation of disease is to make of medicine a science and to be a science it is necessary that there should be a certain degree of exactitude in our knowledge It is not easy to define exactly what means should be employed to make such a subject as medicine a science Each science has to be pursued by methods peculiar to itself and those familiar with the methods in one science are not capable of determining the methods best fitted for conducting investigations in other sciences Medicine is so distinct from all other sciences that no one unless engaged for a long time in its practice can fully understand its peculiar features and the need for methods specially adapted to its pursuits It has scarcely been realized even by those who are engaged in some branch of medicine how complicated a matter it is that there are fields absolutely necessary to its purpose which have so far been hardly touched and that there are members of the profession who have opportunities for the prosecution of research essential for the advancement of medical knowledge whose services have not been employed

Many sciences pass through stages during which they are but a mass of facts without system and arrangement clouded by beliefs and superstition Medicine has not yet thrown off much of the credulity that has hampered its progress and as yet the facts upon which it is based have not been differentiated and classified with that accuracy which is necessary before it can become a science It is necessary therefore from time to time that those who are engaged in the practice of medicine should pause and ask themselves if the object they aim at is being pursued on the right lines

The Progress of Medicine during the Past Fifty Years

The methods of investigation and the type of individual who prosecutes research have altered during the last fifty years Before that time the investigator was a man engaged in medical practice who recognizing in his patients problems that needed solving sought their solution by experiments conducted by himself or under his supervision This was the method pursued by such men as Harvey Hunter Jenner and Lister This type of investigator has almost disappeared and research has passed mainly into the hands of the laboratory worker This has been due to the elaboration of laboratory methods It is readily conceivable that any new country when it is first opened up will reveal a great many new features The development of laboratory methods had yielded a remarkable number of new facts and greatly advanced our knowledge The perfection of mechanical instruments for the examination of the body during life and of the tissues after death has been of the greatest service Moreover the germ theory of disease has thrown such a flood of light upon many diseases that the impression has been made almost universally that it is only by laboratory methods that progress in medicine towards a science can be made To such an extent has this conception prevailed that distinguished laboratory workers can assert without fear of contradiction that in the future progress in medical knowledge can be made only through the laboratory The outcome of this conception is seen in the manner in which research in medicine is encouraged The various governments as well as wealthy donors desirous of helping humanity by the relief of suffering give liberally for this purpose Naturally they turn to medical authorities for guidance and these invariably direct that the money should be spent on laboratories Hence in all countries we see magnificent buildings erected and able men appointed for the carrying out of research To these laboratories are attracted all the brilliant and able among the younger members of the medical profession As generation after generation is brought up under the guidance of the laboratory worker the belief becomes established that on these lines alone can medical research be advanced and other lines of investigation are neglected

Underlying all this seemingly reasonable belief there lies a fallacy Investigators are now specially trained for their work under men who have spent their lives in the laboratory The pursuit of knowledge tends to assume ever more and more an academic character with little reference to the problems confronting the doctor who practices medicine This is in contrast with the methods pursued by the great pioneers whose

names I have mentioned Laboratory workers now get a limited view of disease and we must recognize that their opportunities permit them to see but a very small part of the field of medicine

The reaction of these views upon medical practice is seen in the breaking up of clinical medicine into a series of specialities The patient s examination is not to be restricted to one intelligent practitioner but he must be scrutinized by a number of specialists Thus when a patient consults a physician the physician not content with his own examination sends him to a series of specialists and each of these sends in a report dealing with the organ or method in which he specializes The physician studies these reports and is supposed then to be in a position to treat the patient This method seems so learned and thorough and it has so impressed the community medical and lay, that it threatens to become a necessary procedure in the examination of patients for we find not only physicians in their private capacity practicing it and medical men associating together for the purpose of carrying it out but we find distinguished physicians urging its adoption by the state

This procedure seems so reasonable that it is difficult at first sight to see wherein the fallacy lies That it is fallacious there can be no doubt for otherwise one would despair of the future of medicine It is manifest that if humanity at large is to benefit by medical progress the bulk of the people would fail to receive adequate medical provision by this method It is only a few that can afford the high prices that such specialists charge If institutions even under the government are started only a limited number of the people can be reached Anyone who has practiced in a large community knows that such a scheme would have little effect for many patients are bedridden and the number of ailing people is so great that no institutional means could examine them Moreover to such an institution the cases sent would not be necessarily those that were most in need of help The type of case sent would be those who were manifestly ill usually with some definite sign which indicated that the disease had already caused destruction or alteration of tissue The cases in the early stages before these things happen would not likely be sent and if sent their ailments would not likely be recognized for the phenomena created by the early stage of disease are not revealed by mechanical means or laboratory methods The physician trained in the laboratory or hospital ward can recognize neither the mechanism of the production nor the significance of such symptoms as arise in the early stages of disease

Furthermore granted that an exhaustive report comes in from specialists who deal with the examination by means of x rays blood-

pressure instruments electrocardiographs bismuth meals test meals blood counts urine analyses microscopic and chemical examinations of the blood discharges and excreta and other methods for it is manifest that there is no standard that can limit the number of specialists who is qualified to assess the value of all these reports? The effect of disease is rarely limited to one organ in many cases the change in one organ is secondary to conditions elsewhere The specialist whose horizon is restricted to his particular subject is incapable of recognizing the remote causes and effects Suppose a physician directs these researches the very fact that he has had to call in the help of the others implies that he is not able to detect the phenomena produced by disease and if he is not capable of doing this how can he be qualified to assess their value? As a matter of fact the profession have not yet recognized the importance of this feature the assessing of the value of symptoms while in the practice of medicine they have not employed the appropriate methods by which the knowledge can be acquired

The Life History of Disease

The best way to understand how medical investigation should be pursued is to appreciate the defects in medical knowledge and to do this the life history of disease in the body and the phases that have been studied so far should be considered The onset of disease in the body is invariably insidious and causes little disturbance to the economy and no visible sign of its presence By and by the patient becomes conscious that all is not well with him and there is a loss of that feeling of well being which accompanies the healthy state Disagreeable sensations arise at first vague but later they become more definite and so urgent that he seeks advice Still no evident sign of disease may be perceived on the most careful examination The disease situated in some organ as it continues to advance modifies the tissues of the organ so that a physical sign is produced and its presence detected The course here after varies it may end in death or in impaired health or being of a temporary nature in recovery The course of the disease may be a matter of days or of many years but the general characteristics are the same

Doctors detect the beginning of disease by the presence of symptoms Hitherto in clinical medicine the chief progress has been made in the minute study of disease after it has produced a physical sign or after the patient has died that is to say after the tissues have been damaged It would not be far wrong to describe the last fifty years of clinical medicine as being the era of physical signs

Early Stages of Disease

It is accepted universally that the earlier a disease is detected the more amenable it is to treatment It behooves us then to recognize disease in its earliest stages If careful consideration be given to the matter the importance of recognizing the early stages of disease will be realized and moreover from the patient s point of view it is vastly more important to observe the early stages of disease than to recognize its peculiarities when it has produced physical signs or when it is found on the post mortem table

What are we doing to discover these early stages? The truth of the proposition that the earlier a disease is discovered the more hopeful it is for treatment may be admitted but it has never been realized how little is done to provide the necessary knowledge to understand disease at this stage

In the recent past research has been restricted chiefly to laboratories and in a less degree to hospital wards Consider the stages of disease that are studied there It is unnecessary to dwell upon the careful study in the post mortem room as that is a stage which does not immediately interest the patient and does not concern the beginnings of disease In hospital wards we find the patients with disease so far advanced as to present a physical sign and we all know what time and care is spent on teaching the physical signs Little interest is excited in the student unless there is something he can either see hear or feel with the result that the well trained student leaves the hospital convinced that he has grasped the essence of medicine because of his ability to detect a physical sign and to know the mechanical basis of its production Moreover in the more advanced schools where there are clinical laboratories it is usually to the wards that he is attached This gives the opportunity of confirming the knowledge of the cause of the physical signs and stamps the impression on the student of the essential importance of physical signs We see therefore that disease when it has reached an advanced stage or after it has killed the patient has been thoroughly studied

But what of the stages that preceded? What of the time it may be years of the gradual progress of disease before the production of a physical sign the time when the disease was amenable it may be to treatment or more amenable to mitigation than in the later stages? The patient in the early stages shows no objective sign but he has a definite sensation which tells him that all is not well We all know that such patients go to the out patient department Here we have the younger members of the hospital staff men who have been trained in the hospital wards where the training has made them adepts in the detection of

physical signs What is their attitude? I have visited many hospitals in different countries and the procedure is wonderfully alike wherever I have gone a patient with no physical sign receives as a rule little consideration but when a physical sign is detected he may be sent to the hospital ward This attitude toward a patient without a physical sign is revealed by the scant knowledge we possess of the symptoms in the early stages of disease

It will be granted that subjective sensations are the earlier signs of disease but so far the profession have been so little trained in examining a patient when the disease presents only subjective sensations that the out patient physician has not known how to set about the examination The reason why I make this statement is that the sensations of a patient have never been studied with the care and precision which would enable any teacher of the present day fully to appreciate them

There is not a single sensation which man is capable of experiencing that has been thoroughly investigated Until that is done we shall be incapable of detecting the early stage of disease and it is because this has not been done that I state that the out patient department has not yet been fully utilized Take the most universal of all sensations that of pain a sensation which if understood would reveal the early stages of disease in a large number of cases Yet we are ignorant of the most elementary facts necessary to its understanding We do not even know the tissues capable of producing pain and we have but the slightest knowledge of the nature or kind of stimulation that can induce pain We are to a great extent ignorant of the mechanism by which it is produced and of the laws governing its radiation we have no knowledge We know for instance how informative the spread of pain is in heart disease or renal colic because the distribution of the pain is so remarkable but the distribution is equally informative in many other diseases of which we know little or nothing As one who has labored much at the subject I assert that once we have discovered all the facts concerning pain a stride forward in our knowledge of clinical medicine will have been made which will lead to some of the greatest discoveries in medicine What is true of the neglect of the study of pain is true of every other ensation such as exhaustion giddiness faintness palpitation nausea heartburn and breathlessness

It is evident that the study of the early stage of disease is of the very first importance that it is fraught with difficulties and that the recognition of the nature of the disease is infinitely more difficult at this stage than when a physical sign is present It will be necessary to alter the practice in hospitals At present the easily discovered stage of disease and the most hopeless for treatment is by custom handed over to

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the view that the toxins from intestinal stasis lowered the vitality and rendered the individual susceptible to infection I reconsidered my series of cases of consumption and found that a considerable number had been under my care for years suffering from gastric ulcer a condition which Lane maintains is itself secondary to the intestinal stasis A simple illustration may help to give a clue to the mystery still surrounding consumption A man suffered from a pustular eruption in his hands and arms and consulted a bacteriologist who examining the pus microscopically detected an organism He cultivated the organism and made a vaccine from it This he injected into the man The treatment was persisted in for six months and there was no improvement The man consulted another doctor who found he was suffering from scabies and promptly cured him

There are several morals to be drawn from this experience but the one that is appropriate here is the suggestion that the failure to cure consumption by all the elaborate means at our disposal is probably due to the fact that the tubercular process like the pustular eruption is a superadded disease and the proper line of treatment would be the removal of the primary cause of impaired health *Inasmuch as it is now known that a great many people have a tubercular infection* and never suffer from consumption or other serious tubercular disease it is manifest there must be some other factor than the tubercle bacillus The recognition of this factor can be attained only by the study of the patient before he shows any signs of consumption and the opportunity for doing this exists neither in a laboratory nor in a consumptive hospital but is afforded the family doctor

The Classification of Diseases

The reason given for the need of a body of specialists to examine one patient is that medicine is becoming such a complicated concern that one man is incapable of understanding all its phases This view should at once arouse the suspicion that the pursuit of medicine is not on right lines for the more a subject tends to become a science the more it becomes simple and easy to understand That this should be so a little consideration will render clear A great number of phenomena may be perceived and so long as they are isolated there may be a difficulty in studying them while their individual qualities form the only points for observation But when they are viewed as the manifestations of a common cause then they can be grouped or classified according to natural affinities and their presence and peculiarities can be accounted for easily This is seen in the evolution of such sciences as chemistry botany and astronomy

the experienced physician while that which is most difficult to diagnose and the most hopeful for treatment is placed in the hands of the least experienced These conditions need to be reversed

Secondary Diseases

There is another matter that has never been clearly understood and that is the aspect of disease as presented to the family doctor Those whose experience of medicine has been limited to the laboratory the hospital ward and the consulting room have no idea of the difference between their practice and that of the general practitioner I may point out that the bulk of the general practitioner s patients present none of the physical signs that were taught him in hospital The complaints are chiefly subjective in character and the physical signs of an elusive and evanescent nature that were overlooked or ignored in his hospital experience I have already said that these indicate the early stage of disease but many do more than this they indicate the presence of some affection which in itself may be of little moment but which may by lowering the vitality of the patient prepare him for the onset of other more serious diseases When engaged in general practice I was struck with this difference in the character of the complaints and as time went on I found that the symptoms to which I had paid little attention frequently were evidences of the onset and progress of serious diseases or diseases appeared in other organs remote from the site of the original complaint Thus in an analysis of one thousand consecutive cases there was a vast predominance of digestive troubles but the full extent of this predominance could not be made out as many patients suffering from diseases elsewhere gave a history of early digestive trouble In later years in consultation practice in London I saw many cases of heart affection and I found a large proportion of the cardiac disabilities were secondary in development to intestinal affections In seeking an explanation for this I became aware of Arbuthnot Lane s views and found in my own experience much to support them

It must strike everyone that notwithstanding the enormous amount of work and money that has been spent on the study of consumption we are still far from understanding its real cause or cure It is manifest that there is more in the matter than the presence of the tubercle bacillus It had long seemed to me there was another factor because when I reviewed all the cases that occurred in my family practice I found that every one had suffered from other complaints years before the outbreak of consumption I was at a loss to understand whether this was due to a latent infection or to a predisposing complaint When Lane put forth

in the fact that we are not yet in a position to know the meaning and significance of the symptoms of disease

The Classification of the Symptoms of Disease

The presence of disease is revealed by certain manifestations which it produces and which we call symptoms It is therefore incumbent that these evidences of disease be studied with the greatest care Considering that the account of every disease described in textbooks consists of a record of symptoms and that there are large volumes published specially directed to symptoms it might be assumed that this subject at least had been thoroughly investigated No doubt a great deal of labor has been spent *in finding symptoms* and an enormous number of *symptoms have been recognized but the data thus accumulated have never been analyzed and systematized properly so as to bring out the* full significance of symptoms and progress will be hampered so long as the significance of individual symptoms is not understood At present symptomatology is so confused that the information which symptoms are capable of giving has not been appreciated It may be taken for granted that until symptoms are classified on a basis having reference to the principles underlying their production medical progress will be delayed

I have referred to the fact that the past fifty years has been a period devoted to the recognition of physical signs There is much more required than the detection of such signs As a rule a physical sign merely demonstrates that there is something abnormal in the condition of the organ and it rarely gives information of the functional efficiency of the organ Phenomena provoked by impaired efficiency have received relatively little attention and there has been no clear differentiation between the symptoms produced in these two ways There *is another group of symptoms* which is entirely missed by the laboratory worker and *production of* which has been realized *only imperfectly by clinical observers and that is the group of symptoms produced by the stimulation of the central nervous system by the diseased organ* I have referred to the lack of knowledge concerning pain In addition to pain there are a number of other symptoms which indicate clearly the region in the *central nervous system stimulated by a remote organ It never occurs* to the average clinical observer that the phenomena by which he recognizes many diseases are produced by an irritable focus in the spinal cord The symptoms in appendicitis for instance are mainly and in many cases entirely the outcome of such a focus Thus the situation of the pain the hyperalgesia of the skin and deeper structure of the external body wall the increased reflexes of certain muscles and the tonic con

The advance of medicine so far has not permitted diseases to be classified on any sound principle Medicine is still in that stage when it consists of more or less disconnected facts Diseases themselves are not clearly recognized and often the symptoms they produce are mis taken for the disease itself Such classifications as exist as that based on the affections of separate organs imply a limited outlook and a failure to recognize the fundamental principles involved in the production of disease Some glimmer of the true nature of what a scientific classi fication should be is to be found in taking a broad outlook on such a con dition as disease of the arteries Where there is a general affection of the arterial system little evidence can be obtained from the examination of the arteries themselves except in advanced degeneration as in aneurism The evidence of arterial disease is shown not by observing the arteries but by recognizing the perverted functions of a great variety of organs As the blood supply of these organs is diminished the impaired nutrition produces effects on the structure of the organs and on their functions In some people these effects are more pronounced in one organ while in other people other organs are more affected In this way we get a representation of a great variety of diseases while in any given case the organ whose symptoms are the most in evidence dominates the field and custom associates the patient s state with these dominant manifestations Where organs have a variety of functions as the kidney heart and brain the effects of the impaired nutrition may affect chiefly one or more of these functions and then we get the disease of the organs split up into different varieties and these varieties are called diseases and named according to the disordered function whose symptoms are most in evi dence But even in such an illustration we realize only part of the true state of affairs for there is some underlying cause producing the arterial disease We do know that in some cases syphilis may be an agent and there is a great variety of other conditions assumed to be the cause but most of these assumptions are little better than guesswork as the methods of study hitherto pursued are incapable of bringing the real causes to light Hence we get the position we are in at present a vast accumulation of data with no clear conception of their significance The disadvantage of this confused accumulation of disconnected or imper-fectly related facts is shown in the measures taken to combat disease particularly in the field of therapeutics Anyone who seriously studies the attitude of the profession towards remedies will find great dif ferences of opinion among authorities some having faith in certain remedies others faith in other remedies and others again with no faith in any From this the conviction arises that there is something at fault in the conception of medicine This misconception will be found to lie

in the fact that we are not yet in a position to know the meaning and significance of the symptoms of disease

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traction of some part of the musculature and the abdominal wall with in some cases great irritability of the bladder point to an irritation of the spinal cord in a well defined region This irritable focus, no doubt arises from a peculiar stimulation worked by the diseased appendix The symptoms in angina pectoris and of certain diseases of other organs are produced in a similar manner A study of this phase of the problem is needed badly

The Assessment of the Value of Symptoms

The final and most important of all branches of medicine is the assessing of the value of symptoms As soon as a doctor is engaged in general practice he finds out the importance of this aspect of symptomatology After detecting a sign the patient s inquiry expressed or implied is naturally—What is going to happen to me? Is this a sign of disease that will shorten my life or cripple me? Does it call for treatment or is it amenable to treatment? The answers imply a knowledge of symptoms which no hospital or laboratory training can ever completely supply and yet it is the most important of all forms of knowledge if we are ever successfully to combat disease

This knowledge of how to assess the value of symptoms so absolutely necessary to the progress of medicine distinguishes clinical medicine from all other sciences and all other branches of medicine For its acquirement, methods and opportunities peculiar to itself are necessary While its importance and even its cardinal necessity are widely recognized yet the methods by which this knowledge can be acquired have not yet been understood It has been assumed tacitly that this knowledge has already been acquired and that it is a field of knowledge that requires no special training for its acquisition This however is a great mistake We can easily find evidence of the failure of medicine from this lack of knowledge At this time of national stress when every available man is called upon for war service the burden is thrown upon the doctor of determining the fitness of individuals The military medical authorities thought that the knowledge was easily acquired and that any qualified man however young and inexperienced was capable of undertaking the work To assist them certain regulations vague and often misleading were drawn up It is now everywhere acknowledged that the results of recruits' examinations have been so unsatisfactory that radical changes have had to be made and this has resulted from the fact that the knowledge of how to assess the value of the most ordinary symptoms nowhere exists Even in life assurance where the most experienced members of the profession are engaged the basis on which the prospect of life

is valued when some abnormal sign is detected is to a great extent a matter of guesswork. We can see that by reading the books of those who reckon to guide the profession in such matters. Occasionally one physician more critical than usual realizes this and describes his limitations. Thus Sir William Gairdner in discussing the matter in relation to heart murmurs states, "Whether any data can be procured that will enable our successors to deal with cases of extra risk—we have none and so deal with them either by loading or rejecting or shutting our eyes." How true this is can be verified by anyone who turns to a textbook to find out the prognostic significance of the simplest and most obvious signs. When it is borne in mind that such signs daily are confronting the general practitioner and that the question of assessing their value is arising continually, it will be recognized that the matter is one of urgent concern. Nevertheless it is a matter dealt with in so vague a manner that no clear information is anywhere to be had.

But the defect in the knowledge hampers medicine in every way. There are people who, desirous of keeping in good health, reckon that if they are periodically examined by a doctor they may be prevented from falling ill. But more harm than good may be the outcome, for if some aberration is detected, it may be a shadow in the lungs when examined by the x-ray, or a murmur or irregular action of the heart, the doctor, unable to assess the value of these signs, may give such warnings as seriously to disturb the patient and put him to endless trouble and expense to avoid an illness that was never likely to arise. When there is distinct evidence of an active disease the same uncertainty prevails. We all know that many patients with such diseases as gastric ulcer or appendicitis recover without operation procedures. There are nowhere to be found clear indications when to operate and when not to operate. Some surgeons would remove every suspicious appendix because, though they recognize that some are without danger, yet being unable to distinguish them from the dangerous, they prefer that the patient should not run the risk. What is this but an acknowledgment that they cannot assess the value of the symptoms? When such a surgeon says that the symptoms are not sufficient to serve as a guide, he but deceives himself, for the data are there, only he is unable to interpret them.

The Opportunities of the General Practitioner

It is manifest that if symptoms are ever to be properly valued it can be done only by those who have the opportunity to watch the individual patients through long periods of time, who see the disease at the earliest

traction of some part of the musculature and the abdominal wall with in some cases great irritability of the bladder, point to an irritation of the spinal cord in a well defined region This irritable focus no doubt arises from a peculiar stimulation worked by the diseased appendix The symptoms in angina pectoris and of certain diseases of other organs are produced in a similar manner A study of this phase of the problem is needed badly

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The chief use of laboratory methods is to throw light on the manifestations of disease which can be perceived by the unaided senses Once any particular method has given help in elucidating a sign or symptom it need not be employed in practice though it may be used for demonstration purposes in teaching and for the prosecution of further inquiries It should therefore be the aim of those who have devised some technical method to hasten to get rid of its need for employment in everyday practice The importance of this is manifest If for instance a bacteriologist discovers an organism which produces disease in man he should not limit his observation to studying its peculiar behavior in culture media or in guinea pigs but should recognize the manifestations of its presence when it has gained entrance into the human body It must be evident to everyone that if bacteriology is ever to have its full influence on medicine other methods of investigation must be pursued besides those which are undertaken in laboratories The vast majority of the population cannot have the benefit of laboratory investigation nor is it necessary that they should have for this reason that on the entrance of the microbe into the human body certain phenomena are produced and these phenomena are peculiar to the individual microbe We infer for instance that measles scarlet fever and smallpox are all due to microbic invasion and although the microbes have not been identified the evidences of their invasion are well known The invasion of the body by other microbes will give just as clear evidence only as yet we do not know how to search for and recognize the evidence as pointing to that organism as the cause

The use of special methods can be *superseded in a great many cases* It is stated by those who advocate the *examination of patients by specialists* that their heart s action *should be recorded by means of the polygraph or electrocardiograph* These *instruments undoubtedly have* been of the greatest value *in differentiating the different forms of heart irregularity* Beyond this they *have failed to shed any light of practical* value By carefully *relating the records obtained by these instruments* with the signs revealed by *the finger on the pulse* by auscultation and other simple means the *different irregularities can now be recognized* without the aid of *these instruments* and if *so recognized* they *need no* longer be used These *instruments will always be of use for teaching* purposes *and for the investigation of obscure irregularities and the action* of remedies *but only in very exceptional cases will they be required in* practice

If in other conditions a systematic *attempt be made to correlate the* symptoms perceived by *the doctor s unaided senses with the results of* observation made *by elaborate methods evolved in the laboratory the*

stage, or even before its inception and who can observe its progress through all the vicissitudes of life. Manifestly that cannot be done by the worker in a laboratory or in a hospital ward. On the other hand consider the opportunities of the general practitioner. He is the only individual in the medical community who has a broad outlook on medicine whose life work gives him the opportunity of seeing all parts of medical knowledge in its true perspective. He sees the conditions which predispose to disease he sees its inception and the course it pursues when it is amenable to medical treatment or passing to the time when it calls for surgical interference. He sees the after effects of the operation when the surgeon may claim it as a success. If he cares to inquire into the symptoms of disease he is brought into contact with every special department and has opportunities for estimating them at their true value.

Yet the general practitioner has no say in medical education or research or even in making the laws which bind him to an unintelligent performance of his duties. There are fields of research which block the advance of medicine which can be worked only by him. Yet what is done to encourage him? Money is poured out for research but no one ever thinks of giving him a grant or helping him to make use of his opportunities.

The Place of the Laboratory Worker in Clinical Medicine

It has been a misfortune to clinical medicine that the laboratory worker has been allowed to dominate the field of research. In many cases he has gone after purely academic problems leaving unrevealed a great many phenomena which baffle the physician in his work. The faith in an involved technique has resulted in the simple and easily recognized manifestations being too often ignored while those that are revealed by some elaborate mechanical implement are extolled as being the more scientific. This view has been forced upon me by studying the attitude of the profession towards heart failure. Over fifty years careful study of this matter has revealed to me that heart failure can be perceived only in its early stages by recognizing the sensations evoked by the patient in his response to effort. These are varied and at first difficult to distinguish from sensations due to other conditions. Nevertheless a long continued study enables one to get a true comprehension of the heart's efficiency. Yet we find the vast bulk of investigators unable to recognize these very simple manifestations placing their trust in mechanical methods never realizing that these instruments probably cannot reveal what is essential in the study of heart affections—the efficiency of the heart muscle.

III

THE HERITAGE OF MODERN MEDICINE

By WILLIAM B JOHNSTON

MANY of the *facts upon* which the practice of medicine is based are as old as the history of the human race itself but the ever widening stream of intellectual and social activities scientific and altruistic embraced within the term MODERN MEDICINE had its sources in the cultivated classes of Greece and among the simple folk of Palestine Hippocrates the friend of poets and philosophers was the first physician to free his own mind and the minds of his contemporaries from the inherited obsession of the divine or demon origin of disease and to lay the foundation of modern medical and surgical science The organized care of the sick and of the incapable was the direct outcome of the teaching of Christ and His disciples

The earliest historical records picture the practice of medicine entirely in the hands of the priests or priest physicians who as interpreters of the *will* of the unseen gods and goddesses claimed to possess the most potent charms and therapeutic measures Magic was more powerful than medicine There is abundant proof however that in India Assyrio-Babylonia and in Egypt there gradually grew up a body of lay physicians who were in excellent standing in the community who were protected by law and were even maintained at the expense of the state Medical instruction was given in the temples or in schools attached to the temples which were the forerunners of our modern universities The immemorial *custom of* committing to memory those parts of the sacred writings and traditions which dealt with medicine and in learning the rites and incantations appropriate to the performance of operations and to the administration of drugs was supplemented by observation of the sick who came to consult the priests or to sacrifice in the temple

Egyptian specialists with their multitude of salves and medicinal preparations were celebrated throughout the Eastern Mediterranean and were in demand among their Assyrio Babylonian neighbors whose practice of a crude sort was much concerned with priestly interpretations of the stars and with the ritual of examining the viscera of sacrificial

same result will be attained whether these involve instruments like the x-ray or chemical or microscopic examinations. Of course, there will always be some cases where these methods will help, just as there will always be a residuum on which they will fail to shed any light.

Conclusion

In dealing with the future of medicine in this manner the object is to call attention to the defects in our knowledge. If it is once grasped clearly and definitely where there is a lack of knowledge, the first step is taken to make good that defect. Where there is an absence of a clear perception of the deficiencies in knowledge, even if it is recognized that our knowledge requires supplementing, the efforts taken to supply the deficiencies are certain to be so ill directed that much labor will be spent in unprofitable undertakings. From the foregoing considerations it can be inferred that there is an urgent call to the clinical investigator to view his position from a standpoint different from that to which he has been accustomed. There is a great field still unexplored for the detection and for the assessment of the value of symptoms recognizable by the unaided senses, or by simple mechanical aids. The class of investigators must be enlarged to include those who have the opportunities of seeing disease in its earliest stages. The clinician must take a part in the laboratory investigations in order to solve the numerous problems that will arise if he sets himself to find out the significance of the signs of disease. If he does not himself actually carry out laboratory experimentation, he must at least suggest the theme or direct the method.

This does not imply the supersession of the laboratory investigator, but rather the extension of the laboratory conception to include the man who comes with a problem direct from the practice of medicine. This calls for the closer association of the clinical observer with the laboratory worker, so that on the one hand the clinician will be enabled to understand the mechanism of the symptoms of disease, while on the other hand he will be able to detect in the human body the signs which correspond or are related to the phenomena discovered by the laboratory technician.

deign to bring about a cure there were gradually formed in the temple neighborhoods groups of those lay physicians the Asclepiadæ who claiming descent from Æsculapius and being inheritors through many generations from father to son of the Hellenic medical traditions had long practiced their art among the Greeks Between them and the priests there existed no unfriendly rivalry or competition They were free to follow cases under treatment within the temple and to consult the votive tablets records of cures placed in the sanctuary by generations of devout and grateful pilgrims These groups gradually increasing in size and in importance and admitting into their society all who wished to become physicians formed schools or guilds where the theories and practices of the day differing slightly in each locality were taught to individual pupils by discourses and at the bedside The famous so-called Hippocratic oath to which all students had to subscribe before being admitted to membership in the society of the Asclepiadæ witnesses to the seriousness of purpose and to the high ethical standards of these early physicians

The tendency to philosophize inherent in the Greek mind and the eminence of the philosophers many of whom were also physicians colored the teaching in all the schools At the Greek colonial town of Croton in southern Italy Pythagoras who spent many years in Egypt taught in addition to the importance of understanding the structure and functions of the body a philosophic doctrine tinctured with Eastern ideas of metempsychosis and the prevalence of demons and other mystical beings as the causes of disease Empedocles in his attempts to reach the four essential elements influenced profoundly the current conceptions of physiology and pathology

It was into this world of active speculation where philosophy and medicine were inextricably entangled that Hippocrates the son and grandson of distinguished physicians tracing their ancestry to Æsculapius himself was born Genius can develop in a desert but the richer the soil the more luxuriant and the more perfect will be the growth Fortunately for the world Hippocrates was from his earliest years surrounded by influences which enabled him to become not only a great practitioner of medicine and surgery but one of the most high minded modest kindly well balanced and intellectually fearless men of the world The end of Greek education was not technical training but the harmonious development of body and mind The study of music and of the poets was intended to inspire lofty emotions to soften and to humanize the soul Rhetoric which included training in eloquence and the study of ethics and politics sought to arrive at clear conceptions of the basic principles of conduct to induce clear thinking and a careful

animals On the Indian peninsula practical instruction in surgery, the acquiring of manual dexterity by operating upon bladders, upon gourds and upon the stems of plants developed a proficient class of surgeons who with the help of narcotics successfully performed difficult operations Influenced by his many years in Egypt Moses in creating his ideal state placed the supervision of the public health in the hands of the priests who even exercised the powers of sanitary inspectors Meat inspection so important in the life of the Jews was probably a development of the Babylonian ritual gradually introduced into the sacred law after the Babylonian captivity

Though warped and distorted by superstitious beliefs these early civilizations showed in addition to their extraordinary skill in art architecture and engineering a keen sense of justice and a marked capacity for administration Their point of view in regard to the ordinary affairs of life greatly resembled that of the present day, and though detailed evidence is slight we can conclude that in their hands the practice of medicine was not entirely divorced from careful observation intelligent consideration or from sane and skillful treatment

It is impossible to say exactly how much of this Eastern medical lore and practice was known to the ancient Greeks In common with all early peoples they believed in the supernatural origin of disease evolved a class of priest physicians and depended for the cure of their ills upon sacrifices to their gods and upon the interpretation of dreams and omens Unlike the more easterly races however the Greeks showed a very marked tendency to take a more rational and less grotesquely superstitious view of life The Greek gods and goddesses generalizations of human qualities possessed the form and characteristics of human beings and were supposed to take a lively interest in the welfare of their worshipers

The temples built in honor of the mythical God of Medicine the first physician were in many respects large sanitoria where buildings decorations site surroundings and organization combined to create in the most health giving situations an atmosphere of serenity and of hope The attendant priests though disclaiming to cure otherwise than through the divine aid of Æsculapius whose colossal image in ivory and gold filled the inner sanctuary of each beautiful temple placed as much importance upon a carefully regulated regimen of diet baths and recreations as upon the sacrifices and the expectant sleep before the statue of the god

As the apparently dying and incurable patients were excluded from the precincts of the temples and as the God of Healing did not always

many countries Enriched and stimulated by the work and example of Euclid and Archimedes and by the continued efforts of the Ptolemies themselves men of capacity and cultivation Alexandria became the clearing house and point of distribution for all knowledge For the first time in the history of the world anatomy was systematically taught by dissection of the human cadaver The supply of material was abundant Two physicians Herophilus and Erasistratus pupils of Cos and Cnidus made many accurate and valuable contributions to the newly born science of human anatomy They rose to great prominence advanced the practice of surgery and founded schools of medicine which for many centuries continued to attract the students of the world

The Jews who as a race were decidedly opposed to magic of all kinds showed a great aptitude for scientific medicine and flocked to Alexandria They carried with them into Palestine and Asia Minor the standard of Greek medicine and helped to maintain a closer connection between Alexandria and the extensive Hellenic kingdom which Seleucus another of Alexander s generals had established in Babylon and in Persia They helped also at a later date to carry the lore of Egypt and the classical learning of Greece to the new Empire of Rome

Roman medicine like Roman art and general culture was from the first a borrowed product The worship of Æsculapius had long preceded the arrival of the scientifically trained Greek physicians the first of whom Asclepiades a man of wide education practiced in Rome during the last century before the coming of Christ Of the many highly trained and cultivated Greeks who in the first centuries of the Christian Era lived under the protection of the powerful Roman Empire Aretæus Dioscorides and Galen exercised the greatest influence upon the future development of medicine The works of Aretæus of whose personality practically nothing is known show an originality breadth of view comprehensiveness and clearness found only in the writings of Hippocrates He described vividly many distinct forms of disease Dioscorides a military physician who had unusual opportunities for travel throughout the Empire compiled the first Materia Medica a complete list of the medicinal agents then in use with a description of their therapeutic action Galen brought from his birthplace at Pergamum in Asia Minor where there long had been a celebrated school of medicine from travels in Egypt and from the still famous schools of Alexandria a wealth of scientific information and a skill in practice which soon placed him at the head of his profession He was much sought as a lecturer and teacher and his voluminous writings on every branch of medicine summed up the knowledge of his day He made many original contributions to the science of anatomy particularly of

wording of the thoughts expressed Training in the gymnasium aimed to produce a harmonious development of all the muscles to achieve physical perfection

Under the direct supervision of his father as was the custom among the Asclepiadæ the young Hippocrates began his medical studies on the island of Cos his birthplace His naturally acute powers of observation and his definite bent in a practical direction rapidly developed in the congenial atmosphere of the long established and already famous Asclepiad school at Cos The objective investigation of disease the study of etiology and an insistence upon the value of the expectant treatment combined with mild therapeutic measures which distinguished the teachings of Cos from the more subjective methods of the nearby school of Cnidus gave him the foundation upon which he built with such power and effect A further period of study in the stimulating world of Athens then at the height of its glory followed by travel in Thrace Thessaly and Macedonia increased his knowledge of men and of disease and brought him into close contact with currents of contemporary thought and the accumulated knowledge of the past True to the Greek type his mind was constantly concerned with the search for fundamental principles His writings simple forceful and direct give the picture of disease rather than of diseases They include all that was important and essential in the teachings of the schools and declare with a distinctness remarkable for that superstitious and speculative age that disease is the result of natural causes which are to be searched out and considered in the most critical spirit until all sources of error are as far as is humanly possible finally eliminated

The necessary forward step had been taken Following upon Alexander s ambitious conquests the writings of Hippocrates and of his followers were spread over the greater part of the known world setting a standard of professional conduct and of scientific attainment and opposing a bulwark against the still superstitious mental attitude of the East

With the final exhaustion of the Greek creative impulse the center of intellectual life shifted to Alexandria where Alexander s general Ptolemy and his descendants concentrated the trade and culture of East and West Here in the handsome and spacious Museum and Serapeum the spirit of Hippocrates and of Aristotle the son of a physician founder of comparative anatomy and embryology and the second great scientist of the Hellenic Golden Age dominated the minds of Greeks Egyptians and Jews Alexandria offered all the external stimuli to intellectual activity —well stocked libraries and museums highly paid professorships and a large body of students drawn from

many countries Enriched and stimulated by the work and example of Euclid and Archimedes and by the continued efforts of the Ptolemies themselves men of capacity and cultivation Alexandria became the clearing house and point of distribution for all knowledge For the first time in the history of the world anatomy was systematically taught by dissection of the human cadaver The supply of material was abundant Two physicians Herophilus and Erasistratus pupils of Cos and Cnidus made many accurate and valuable contributions to the newly born science of human anatomy They rose to great prominence advanced the practice of surgery and founded schools of medicine which for many centuries continued to attract the students of the world

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the nervous system and attempted by experiments upon animals to investigate the functions of the various organs

Increased familiarity with anatomy enabled the surgeons to make even greater advances than were made in medicine With a variety of efficient instruments they performed major operations resections, and difficult feats in plastic surgery

The Roman genius for organization did not neglect the public health District physicians *archiatri populares* attended the poor and served as a board of consultation in the matter of controlling epidemics The principle of hydrotherapy introduced with the cult of Æsculapius was elaborated until the baths (the gorgeous baths of Caracalla and Diocletian accommodated from sixteen hundred to three thousand persons) became part of the public life At Baden Baden and Wiesbaden at Aix-les Bains and at Bagneres de Bigorre in the Pyrenees at Bath and wherever the Romans found natural springs large establishments were built

The general disorganization of the Empire following the successive waves of barbarian invasion and the persistent infiltration of the Christian faith which antagonistic to everything connected with the ancient pagan world was finally adopted by both conquerors and conquered practically put an end to the long uninterrupted progress in medical organization knowledge and practice The baths certain schools of medicine in Rome and the Western provinces and the institution of the *archiatri populares* were adapted to the needs of the conquerors Under the slightly less disturbed conditions of the Eastern Empire a few men of unusual ability Oribasius and Aetius physicians to the Byzantian emperors Alexander of Tralles Paul of Ægina and John Actuarius collected and arranged the writings of the ancients practiced surgery and throughout the fourth fifth sixth and seventh centuries made original observations upon disease But by the beginning of the sixth century the temples of Æsculapius had long been closed the schools of philosophy abandoned and Greek culture was seeking asylum in Asia Minor and in the kingdom of Persia Throughout the West and along the shores of the Mediterranean the ideals and the wisdom of the Old World had gradually disappeared and all branches of education were passing under the control of the Christian priests

Destructive and obstructive as were these years of constant warfare and emotional upheaval a powerful constructive force had been at work Except in India where Asoka the first great Buddhist king had established hospitals for men and animals no general attempt to care for the sick and unfortunate had ever been made In Egypt and in Babylon it had been the custom to place the sick in the streets where friends

and passers by exchanged experiences with and gave advice to the sufferers In Greece the well arranged and well supplied *iatreia* were usually attached to the houses of physicians and served more for the treatment of out patients than as hospitals The Roman *tabernæ medicæ* were copies of the Greek *iatreia* and the convalescent homes and sick rooms built by the great landed proprietors were open only to slaves and dependents on the Roman estates The army had its hospitals and its stalls for sick horses The early Christian Church had been organized not so much for the purposes of religious worship as for the care of the sick and the destitute and throughout its early history the social service side of its activities absorbed the energies of its rapidly increasing converts Archdeacons deacons and deaconesses administered a communistic charitable organization and the *parabolani* male and female nurses sought out the sick and needy whom the Church cared for and protected Beginning in the poorest and simplest class of society the impulse gradually spread to the upper classes Fabiola a well-to-do Roman widow whose example was followed by others founded a Christian infirmary and cared for the sick in person By the middle of the fourth century the teachings of Christ had so penetrated the Roman world and had gathered such force and importance that large hospitals began to appear The institution founded by St Basil at Cæsarea in Asia Minor was one of the earliest and also one of the largest Special doctors and nurses were in attendance and with its workshops and industrial school it soon reached the proportions of a small town There were hospitals in Constantinople in Antioch in Alexandria and by the sixth century there were hospital foundations in France and in Spain

The inclusion of the monastic system within the Church organization broadened the social service aspect of Christianity Each monastery had its hospice or hostel and even small communities boasted their homes for the aged for cripples for orphans and for foundlings At Cæsarea a special department had been devoted to the care of the lepers and in many parts of Italy and in Switzerland the establishment of lazar houses preceded the founding of hospitals When in the eleventh century after the Crusades this long known and already prevalent disease began to spread at an alarming rate the lazar houses dotted the continent of Europe The religious fervor of the Crusades produced a great increase in the associations such as the Brothers of St Anthony the Knights and Ladies of St John the Lazarists and the Black Sisters who devoted their energies to nursing and such were the strictness intelligence and concentrated effort with which the lepers were cared for that by the sixteenth century the disease had been stamped out

It was only natural that the emotional enthusiasm, the general ignorance of past achievements and the power and prominence of the priests should cause a revival of the sacred or priestly type of medical practice Yet, in spite of the renewed faith in prayers exorcisms, charms and amulets the active interest in the careful study and rational treatment of disease never wholly disappeared Many of the earliest bishops and abbots were physicians They have left careful descriptions of small pox epidemics and it was a bishop who first used the term variola The Order of Benedictine Monks paid particular attention to the study of medicine Alcuin an English Benedictine aided Charlemagne in establishing the Cathedral Schools where as in the Temple Schools of Egypt medicine was taught The Monastery of Monte Cassino near Naples built by St Benedict upon the ruins of a temple of Apollo gradually developed into the School of Salerno the earliest of the many famous European schools of medicine

In the East Nestorius the deposed patriarch of Constantinople removing with his followers to Edessa a fortified Roman outpost and carrying with him the spirit of ancient Greek learning founded both a hospital and a school of medicine The influence of the Nestorians soon spread to Nisibis also a fortified town where under Greeks and under Jews trained at Alexandria eight hundred students are said to have gathered Other similar centers of learning sprang up in Eastern Asia Minor but the persistent persecution of the Christian emperors at Constantinople eventually drove Nestorians and philosophers southeastward until about the year 500 they sought safety at the Court of Chosroes king of Persia

Chosroes I and his son Chosroes the Conqueror the strongest kings of Persia since the days when Artaxerxes and his son had raised their new kingdom on the ruins of the extensive realm of Seleucus were champions of Zoroastrianism the native religion of Persia and were violently opposed to Christianity While waging a constant and eventually suicidal war against the Byzantine emperors they permitted Nestorians and philosophers to settle at Ctesiphon on the Tigris near modern Bagdad and at the long established schools of Gondisapur near the ruins of Susa Since the decay of the kingdom of Seleucus Persia had been more in touch with India than with Greece and at the famous schools of Gondisapur Greek and Indian culture came once more into intimate contact The Nestorians taught and practiced in the hospital and it was here that the conquering Arabs irresistibly spreading eastward found one of the largest and most important centers of Greek culture fused with the medical traditions and practices of India

The Bedouins of Arabia were not a naturally imaginative or religious

race They had no mythology and the religion preached by Mohammed was a simple monotheism the least mysterious of all the positive religions The 'Arabian Nights are of Indian or Persian origin and only the pictures and anecdotes of actual life are truly Arabian To this inherent interest in facts there was soon added a passion for general culture and as their political dominion was established they revived the schools of Alexandria and turned their mosques into free institutions of learning The simplicity of their religion encouraged the growth of a spirit of tolerance Learned men and physicians of all faiths and nationalities particularly the Jews with whom the Arabs had much in common were welcomed and employed by the Caliphs The lay and medical literature of the Greeks Jews Persians Indians and Egyptians was carefully collected translated into Arabic and absorbed with avidity Bagdad and Damascus Alexandria and Cordova vied with each other in securing rare volumes and in founding libraries Abd ar rahman III and his successor Hakam II the most capable of the Caliphs of Cordova had agents in all countries who bought regardless of cost ancient and modern manuscripts whose care added to the labors of copyists, binders and illuminators already attached to the enormous Cordovan library Hakam s court was crowded with scholars from every land, and all branches of learning flourished Thousands of students were attracted to the university In the twenty seven public seminaries of Cordova the children of the poor received an education and centers of learning existed in all the larger towns of Spain While in Christian countries only the priest could read or write these accomplishments were common to nearly all Arabs The exact sciences mathematics mechanics, and physics were highly developed The science of chemistry and its sister science pharmacology were practically reborn A great number of the new remedies and preparations were added to the *Pharmacopœia* and the Arabian works on Materia Medica ranked throughout the Middle Ages with the volume of Dioscorides Apothecary shops were first introduced by the Arabs

The study of medicine was considered an important branch of general culture From the end of the ninth to the beginning of the thirteenth century Arabian physicians from Rhazes and Hali ben-Abbas the Persian to Avenzor and Moses Maimonides physician to Saladin dominated the medical world They were sought as body physicians by Christian kings and even became viziers to the Caliphs Their theory and practice were based upon the works of Hippocrates Galen and Aristotle The elaborate writings of Avicenna, physician in chief to the Bagdad hospital were the standard work of the Middle Ages Albucasis of Cordova published a great medico chirurgical treatise picturing the instru

ments of his day which unfortunately owing to the Mohammedan prejudice against dissection and cutting were being gradually discarded for the cautery Averrhoes also of Cordova was a fearless logician philosopher and free thinker and added to the reputation of those of his race for great independence in the practice of their profession

The practical Arab was quick to grasp the essential usefulness of the Christian hospital development They not only continued and enlarged existing institutions but erected others notably the great Al Mansur Hospital at Cairo which was more elaborate and socially efficient than any under control of the Church Their treatment of the insane whom they regarded as divinely inspired was much more gentle and humane than was that employed by the Christians The decline of the Arabian civilization was as rapid and extensive as had been its rise By the beginning of the fourteenth century the fierce energy aroused by the teaching of Mohammed had burned itself out No great discoveries had been made nor had any far reaching or fruitful idea been born, but many branches of science had been enriched the treasures of ancient learning had been saved and the stagnant intellectual life of Christian Europe had been refreshed and stimulated

The revivifying spirit worked mainly through two channels the medical schools of Montpellier and Salerno If the Arabs took no part in the founding of the famous school of Salerno they had much to do with its development It is probable that the gathering of health seekers in or near the Benedictine monastery and ecclesiastical hospitals of Monte Cassino gave an opportunity to monks and novices interested in medicine to establish themselves in practice in the equally soothing and stimulating air of nearby Salerno The church officials who occupied positions as directors and professors in the gradually evolved school of medicine welcomed the Jews and Arabs from Sicily Arabic translations of the medical classics retranslated into Latin soon formed the basis of medical education and by the tenth century the doctors of Salerno had become so celebrated that their aid and advice were sought by distant sovereigns and by prominent travelers So great was the unprejudiced spirit of intellectual freedom that women were admitted to the profession and even to the professorships Many women became celebrated as medical authoresses

Southern Italy and the island of Sicily parts of the Mohammedan world had been conquered by a powerful Norman prince and this vigorous brilliant and tolerant Norman state soon exercised a decided influence upon the school of Salerno In 1140 Roger of Normandy king of Sicily and Naples promulgated a law that Whoever from this time forth desires to practice medicine must present himself before

our officials and judges and be subject to their decision Anyone audacious enough to neglect this shall be punished by imprisonment and confiscation of goods This decree has for its object the protection of our kingdom from the dangers arising from the ignorance of practitioners A century later Frederick II king of Sicily and Naples and as grandson of Frederick Barbarossa also emperor of the Holy Roman Empire one of the most remarkable personalities of the Middle Ages and an enthusiastic friend to all men of learning irrespective of their creed took an intense interest in medicine He not only renewed the law of his Norman grandfather King Roger in whose kingdom he had spent his early years but drew up a set of rules and regulations *for the study and practice of medicine which in their intelligent comprehension of the needs of the student the public and the profession* set a standard for all future medical legislation A three years preliminary education in logic the then classical course of study had to precede five years devotion to the study of medicine based upon the Hippocratic writings After successfully passing the state examination for which a Latin diploma was granted the young graduate before starting an independent practice was expected to gain a year s experience under the guidance of an established practitioner Those wishing to practice surgery were required to present certificates testifying that they had acquired a thorough knowledge of human anatomy and had spent at least one year in practical surgical work All candidates had *to promise on oath that they would give free advice to the poor and that they would inform the magistrates of mistakes in filling prescriptions made by the apothecaries The apothecaries had to swear that they* would dispense only drugs of known purity and physicians and apothecaries were forbidden by law to form partnerships The preparation of drugs was supervised by inspectors

Frederick s regulations were later adopted by the rival school of Montpellier where on account of its nearness to Spain and the broad minded attitude of the Church Jews and Arabs had early exercised a like influence in stimulating and developing the original Christian hospital and school of medicine Salerno long retained its prominent position as a center for medical studies After a slow and gradual decay it was in 1811 finally closed by order of Napoleon To the Medical Faculty at Montpellier soon were added faculties of Law and Theology and the University of Montpellier though no longer attracting enormous numbers of students and distinguished invalids exists today

The *almost insurmountable prejudice against dissection of the human* body *which had expressed itself in legal ordinances* was *the only great* handicap to the progress of the thousands of keen minded *medieval*

medical students and professors Even the bold Frederick was not able to furnish except once every five years the material necessary to the requirements that he himself had laid down The carcases of bears monkeys pigs and dogs revealed only approximate truth and the Anatomy of the Pig by Cophо the Jew of Salerno had to serve as the student s handbook During the great plagues bodies were frequently opened in the hope of discovering the cause of the devastating pestilence and the law occasionally sanctioned post mortem examinations in suspected cases of poisoning Whenever a body could be procured by stealth hurried dissections were carried out In 1316 Mondino di Luzzi professor at the University or Studium Generale of Bologna, circulated his Anatomia or practical guide to dissection and little by little the students not satisfied with lectures and scholastic discussions of the medical classics and desiring first hand information, demanded a relaxation of the proscriptions Popular prejudice was not so easily overcome In 1368 the Senate of the Republic of Venice issued a decree that a dissection should be performed once a year at Padua Montpellier later received this legal permission and within a few years this privilege was granted to the University of Lerida in northern Spain The bodies were those of criminals By the beginning of the fifteenth century dissections became more common at Bologna and the third, fourth- and fifth year students who paid the expenses of procuring preparing and burying the corpse were invited to attend the ceremony being so arranged that before the completion of his course of studies each student should have had the opportunity to follow the dissecting of a female and two male bodies Where the bodies of criminals were lacking the corpses of those who were not natives of the town were used By the middle of the century the authorities of Bologna Padua Ferrara and Pisa regularly supplied two corpses a year to the universities At Paris Oxford Cambridge Prague and in the universities of Germany dissections were not arranged for till at a much later date The universities of Bologna and Padua were the first to build anatomical theaters and Italy long held the lead in the teaching of anatomy For two hundred and fifty years however dissections remained on account of their infrequency among the most important and thrilling events in university life John Evelyn who in 1645 began at Padua a course of lectures in ' physic and anatomy by the most famous professors in Europe records in his diary that he was 'present at the famous anatomy lecture celebrated here with extraordinary apparatus lasting almost a whole month and that during this time he saw ' a woman a child and a man dissected with all the manual operations of the Chirurgeon on the human body

These ' operations of the Chirurgeon were undoubtedly at this date extremely varied and interesting Though the Church for some time had forbidden the practice of surgery to the clergy and had by so doing cast a social stigma upon those who used the knife interest and progress in this branch of the profession had not been stifled A few French and Italian operators had compelled recognition not only for themselves but for their art Guglielmo Caliceti city physician (the old Roman *archiater*) of Bologna and later of Verona a university trained man with a wide experience in the hospitals and on the battle field had at the beginning of the thirteenth century boldly abandoned the Arabian cautery His pupil Lanfranchi of Milan going to Paris and associating himself with the Surgical College of Saint Come had with the assistance of his pupils given practical demonstrations in surgery His contemporary Henri de Mondeville an original and picturesque figure had forcibly described the advantages to the surgeon of absolute cleanliness Guy de Chauliac a country boy from Auvergne priest and surgeon educated at Toulouse Montpellier Paris and Bologna and physician and chaplain to three successive Popes of Avignon had compiled his *Chirurgia Magna* in which he described the narcotic inhalations used throughout the Middle Ages to produce anesthesia Branca of Sicily and his son Antonio itinerant surgeons had caused the greatest excitement by their skill in repairing injuries and deformities of the face

In 1543 Vesalius the vigorous and self reliant Belgian after five years as public prosecutor of Padua under Sylvius professor of anatomy had published his beautiful plates and woodcuts of the human body and was teaching and demonstrating in the crowded amphitheaters of Padua Bologna and Pisa that there were many facts not contained in the works of Greek and Arabian authors The eager spirit of inquiry the desire to study Nature at first hand to no longer follow tradition or to depend upon authority which in the fifteenth and early sixteenth centuries indicated the dawning of the modern scientific era had been nowhere more marked than among the painters and sculptors of Italy Every Renaissance artist had become a realist and a pseudo scientist interested in problems of perspective and of human anatomy Leonardo da Vinci who finally abandoned Art for Science had been a most brilliant careful and discriminating dissector Michelangelo already an old man when Vesalius began to teach knew more of human anatomy than did the professors of the schools The notes and drawings of these two great men unfortunately had not been accessible to inquisitive students and practitioners and to Vesalius alone is due the credit of having placed Anatomy at last upon a firm scientific footing

Surgery had made immediate profit of these new and accurate discoveries which had been corroborated and added to by Vesalius pupil Fallopius The revival of Greek learning which followed the tireless researches of Petrarch and of his indefatigable helper Boccaccio and the arrival in Italy of Greek scholars and original manuscripts from conquered Constantinople had led to a rediscovery of ancient surgical procedures The surgeon of the Renaissance essentially a practical man and not a scholar had received a greater stimulus however from the introduction of firearms which producing wounds unlike any that had ever been encountered forced a recasting of old conceptions and the invention of new methods of treatment No surgeon used the discoveries of Vesalius the new Greek learning and the experiences on the battlefield to greater advantage than did Ambroise Paré the barber s apprentice and surgical dresser of the Hotel Dieu who when opportunity offered developed into one of the great men of France He popularized the works of Vesalius invented many instruments demonstrated the uselessness of cauterization and by reintroducing the ligature which had not been used since Roman times blazed the pathway for future progress in major surgery

During the thirteenth century while the successful campaign against leprosy was at its height the control of the ecclesiastical hospitals passed into the hands of the municipal authorities Many new institutions modeled after the hospital of Montpellier were erected and the custom of using hospitals for the purposes of teaching gradually became more common The impulse given to scientific inquiry by the monk Roger Bacon bore fruit in carefully kept case records which were compiled and circulated by university professors The enthusiasm for Greek learning and the consequent establishment of Platonic academies made a knowledge of the Greek tongue essential to the cultivated physician Thomas Linacre educated in Italy and with Henry VIII and Cardinal Wolsey founder of the College of Physicians published a Latin translation of Galen s original works and Rabelais priest and physician translated the Aphorisms of Hippocrates The invention of movable type which had permitted the publication of semi popular medical works written in the vernacular weakened the importance of classical learning and prepared the stage for the appearance of Paracelsus a man of strong religious feeling and of enormous vitality who possessing the independence of spirit that characterized both Vesalius and Ambroise Paré loudly and combatively asserted the superiority of the personal observation of disease over slavish dependence upon the experiences of Galen Avicenna and the ancients

The breadth and variety of Paracelsus own experiences gave added

force to his teaching He was the son of a learned Swiss physician had been educated at the University of Basle and had spent many months at Swaz in the Austrian Tyrol in the mines and laboratories of the Fuggers the bankers and merchant princes of Augsburg Here he had made an exhaustive examination of metals had discovered zinc made zinc ointment and had formed the conclusion that the aim of chemistry was not alchemy the manufacture of gold but the preparation of medicines He had visited the universities of Vienna and Cologne and the schools of Italy had spent some time at Montpellier and speaking Latin the language of scholars throughout the world had visited Spain and England He had served as barber surgeon in the army of the Netherlands had traveled from the North Sea to the Bosphorus and had served three years as surgeon in the Venetian army

His first teaching in Tubingen and in Strassburg while fascinating to students aroused the antagonism of the settled practitioners and his stay at Basle where he had been called by the Protestants was hardly more successful His crowded lecture rooms where he spoke in German his bedside teaching his kindness to the poor students who lodged at his house and who helped him in the preparation of his mineral medicines and his uncompromising opposition to the accepted matter and manner of instruction aroused the enmity both of the apothecaries and of his Catholic confreres During a students celebration he had thrown the Canon of Avicenna into a huge bonfire burning in the market place of Basle and though he had remained true to the Church his opponents compared him to Luther Persecution and injustice finally led him into publishing a vitriolic reply to his enemies and threatened with arrest he was forced to leave the university He fled to the mountains where believing with his friend Erasmus that the Church should be reformed from within he began to teach religion and to distribute the Bible Again his activities and personality aroused the enmity of the Catholics He had been refused permission to practice medicine in Switzerland and being at last reduced to great poverty he fled into Austria where until his early death (he was killed by a blow upon the head when he was only forty-eight years old) he continued his chemical experiments After much opposition he finally published his Greater Surgery which brought him again into prominence and he was for many years the most widely known physician in Europe His treatise on the diseases of miners was a valuable contribution to clinical medicine and his other writings though permeated with his strong religious and mystical feeling greatly aided the further development of medical chemistry

Great intellectual movements call for great leadership and great leaders require more than the possession of original ideas and intellectual

independence Had Vesalius Pare, and Paracelsus not possessed the added qualities of restless force personal magnetism, and moral and physical fearlessness the dead weight of the past might have continued to paralyze all scientific progress By force of personality these three pioneers broke through the encircling wall of tradition and led their eager followers into a new and living world of progressive scientific activity

CHAPTER I

PATHOLOGICAL PHYSIOLOGY IN INTERNAL MEDICINE

By MARK D ALTSCHULE

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INTRODUCTION

Medical thinking for centuries was dominated by pathological anatomy while abnormal physiology played a relatively insignificant role in the develop

ment of clinical medicine The reason for this was not that anatomy had fundamentally greater importance than physiology but that it had only a lack of data bearing on the latter Anatomists have available for study changes which usually persist for relatively long periods of time which require no special recording methods and which are easily detectable after death Physiologists on the other hand study transient phenomena which can be recorded and in some cases detected only by means of special apparatus and which disappear at death The accumulation of data in physiology therefore was slow until the development of mechanical and more recently optical and electrical methods made possible a constantly accelerating rate of progress At the present time the content of pathological physiology is enormous and physiological concepts dominate many branches of internal medicine Although it is probably true that the physiological approach is more important than the anatomical to the practicing physician who sees rarely the internal organs of his patients it is superfluous to point out that a complete understanding of disease processes is impossible without consideration of the pathological anatomy It is an error moreover to assume that in all instances anatomical changes are important only when they cause functional disorders since much of medical practice revolves about the detection of anatomical lesions before they have progressed to a point where they cause symptoms There are however many disorders in which gross and even microscopic changes in morphology are minimal or absent This occurs most commonly in the endocrine diseases and in nervous and mental disorders endocrinological thinking is largely physiological and the concepts underlying psychosomatic medicine are entirely so

In the present discussion no attempt will be made to consider in detail the changed physiology of specific conditions since these are discussed elsewhere in these volumes Rather it is planned to cover a few more or less neglected topics of general application to a number of diseases in order to call attention to these data and also to demonstrate how the studies of function are important for the understanding of clinical manifestations of disease

Cutaneous Circulation and Body Temperature in Various Clinical Conditions

There are a variety of conditions in which variation in cutaneous circulation influences body temperature in most instances the changes in cutaneous temperature are primarily neurogenic while in others they occur in response to and accordingly modify, changes in body temperature which have occurred already

Fever — Fever may be classified in various ways but for present purposes the following simple etiological scheme will be used

A Endogenous Fever
  1 Fever of exercise
  2 Fever of infection or tissue breakdown
  3 Fever of hypothalamic lesions
B Fever Physically Induced
  1 By heating the body externally
  2 By diathermy or short radio waves

The fever of exercise is a normal phenomenon and appears to be consequent on one hand to a greatly elevated metabolic rate with increased heat production and on the other hand to shunting of the blood from the skin to the muscles with resultant impaired heat dispersal. This type of fever need not be considered here.

The fever of infection or tissue breakdown is one of the manifestations of disease encountered most commonly and accordingly will be discussed at some length. Often it is associated with chills and frequently it is preceded by a prodromal period during which a variety of non specific complaints such as muscular pains, headache, nausea and dizziness may occur in varying degrees of intensity. Defervescence terminates the febrile attack. A bout of malarial chill and fever or that which follows the injection intravenously of typhoid vaccine or other pyrogens is a compressed version of the life history of a febrile illness, and many physiological studies therefore have been made during such episodes; data obtained following the injection of typhoid vaccine are possibly the best controlled. The injection of this vaccine intravenously is followed by four well defined periods, i e prodrome, chill, flush and defervescence.

Fever physically induced, i e by means of lamps, infra red radiation, heating cabinets or electric blankets or by diathermy or short radio waves, has a different life history in that only two phases are detectable, namely flush and defervescence. The flush of fever physically induced closely resembles that of endogenous fever but is more intense and associated with more profuse perspiration.

During the *prodromal phase* of endogenous fever no detectable physiological or chemical change occurs and there is no explanation for the symptoms which occur during this period; the body temperature remains normal. The end of this phase of the febrile reaction is rather sharply demarcated. The next phase, designated as the *chill phase* although actual rigors need not occur, is ushered in by the sudden development of cutaneous vasoconstriction. This is indicated by the pallor of the skin and may be demonstrated on examination by means of the microscope of the capillaries of the nailfold. A discharge of sympathetic nervous impulses originating in the hypothalamus is considered to be the cause of the observed vasoconstriction; the mechanism which gives rise to this reaction

ment of clinical medicine The reason for this was not that anatomy had fundamentally greater importance than physiology but that it had only a lack of data bearing on the latter Anatomists have available for study changes which usually persist for relatively long periods of time which require no special recording methods, and which are easily detectable after death Physiologists on the other hand study transient phenomena which can be recorded and in some cases detected, only by means of special apparatus and which disappear at death The accumulation of data in physiology therefore was slow until the development of mechanical and more recently optical and electrical methods made possible a constantly accelerating rate of progress At the present time the content of pathological physiology is enormous and physiological concepts dominate many branches of internal medicine Although it is probably true that the physiological approach is more important than the anatomical to the practicing physician, who sees rarely the internal organs of his patients it is superfluous to point out that a complete understanding of disease processes is impossible without consideration of the pathological anatomy It is an error moreover to assume that in all instances anatomical changes are important only when they cause functional disorders since much of medical practice revolves about the detection of anatomical lesions before they have progressed to a point where they cause symptoms There are however many disorders in which gross and even microscopic changes in morphology are minimal or absent This occurs most commonly in the endocrine diseases and in nervous and mental disorders endocrinological thinking is largely physiological and the concepts underlying psychosomatic medicine are entirely so

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normal The excessive increase in respiration relative to oxygen consumption which occurs in this phase leads to the blowing off of carbon dioxide so that the respiratory quotient rises and the alveolar air arterial blood and venous blood carbon dioxide concentrations fall appreciably The hyperventilation of the chill phase of a febrile reaction is increased greatly when violent rigors occur but the blowing off of carbon dioxide is not increased above that seen in the absence of rigors since the intense muscular activity of the shaking chill results in a greatly increased metabolic rate with a consequent rise in oxygen consumption and carbon dioxide production Nevertheless the respiratory quotient during a shaking chill rises to or above 1 0 since the fuel consumed is largely carbohydrate The blowing off of carbon dioxide which occurs in the chill phase leads to alkalosis evidenced by a rise in the pH of the blood A parallel increase in the pH of the perspiration and saliva has been noted the latter may account in part at least for the bitter or brackish taste in the mouth which is a common complaint in patients with high fevers Another consequence of severe hyperventilation is a decrease in gastric acidity since the secretion of acid has been shown to vary with the level of blood bicarbonate It is clear therefore that the respiratory changes of the chill phase and their secondary consequences fall into a uniform pattern which can be explained on the basis of loss of normal heat dispersal via the skin when vasoconstriction becomes marked

Cardiovascular dynamics are affected also by the vasoconstriction of the chill phase the degree of change which occurs being roughly parallel with the severity of the clinical manifestations at the time If vasoconstriction is relatively mild the only demonstrable change is a moderate degree of slowing of cutaneous flow demonstrated by a slight slowing of arm to tongue circulation time and a moderate fall in the concentration of oxygen in the venous blood taken from the antecubital or some other superficial vein Cyanosis becomes evident The cardiac output is unchanged or may increase somewhat in response to the increased metabolic demands of the body the rise in cardiac output is however smaller than that of the metabolic rate The vasoconstriction of a mild or moderately severe chill may result sometimes in a rise in arterial pressure of as much as 50 mm of mercury although this reaction is not the rule A severe chill reaction results in a marked decrease in blood oxygen content in the antecubital venous blood and also in blood drawn from the jugular and femoral veins The arm to tongue circulation time may be doubled and the cardiac output may fall by a third or more in spite of the increased oxygen consumption which results from the fever Studies of renal blood flow also show a considerable decrease in that function oliguria or anuria are the rule The arterial pressure usually is maintained by vasoconstriction A severe chill reaction may however result in so much vasoconstriction that the return of blood to the heart is impaired the

on the part of the hypothalamus is however not understood Other evidences of sympathetic activity observed in the chill phase of a febrile episode are the occurrence of a few small beads of sweat about the face and hands, gooseflesh and in many patients a slight rise in arterial blood pressure The cutaneous vasoconstriction somewhat variable initially soon becomes progressive and severe and results in a fall in skin temperature When the skin temperature falls sufficiently, the patient feels chilly or even cold Cutaneous vasoconstriction severe enough to lower the temperature over most of the body to approximately 20° C results in a shaking chill If the patient is in the chill phase but no rigors have occurred, they can be produced by factors which favor vasoconstriction such as the application of a single ice cube to the skin or a blast of cold air This phenomenon may explain the fact that patients commonly ascribe an infection to being exposed to cold what probably happens in many cases is that they are already in the chill phase of the infection and exposure to cold exaggerates the severity and accelerates the course of a chill reaction sufficiently to make it detectable by the patient If shaking chills are present they may be abated or terminated by factors which favor vasodilatation such as antipyretic drugs alcohol and warming the skin externally The occurrence of the chill reaction depends upon the integrity of the nervous innervation of the blood vessels for a sympathectomized limb does not show the characteristic changes though it does shiver

The onset of the chill phase is followed soon by a rise in rectal temperature, which results from an increased metabolic rate initiated by the febrile process itself and is exaggerated by the muscular activity associated with rigors the rise in rectal temperature is greatly accelerated and further exaggerated by the above described cutaneous vasoconstriction Normally approximately four fifths of the heat produced by the body is dispersed via the skin so that impaired circulation through the skin results in the retention of heat In general therefore, chilly sensations or rigors are associated with rapid rises in body temperature the degree of rise varying roughly with the severity of the chill Paradoxically the patient who feels coldest is the one in whom the rectal temperature is rising most rapidly

Certain changes in respiration result from inability of the body to rid itself of heat in a normal manner since an attempt is made to disperse heat by other mechanisms An increase in respiratory rate and minute volume occurs and i far out of proportion to the increase in oxygen consumption caused by the fever so that it is interpreted as a compensatory mechanism in heat dispersal There are no changes in the lungs sufficient in themselves to account for this hyperventilation In addition experiments in animals have shown that perfusion of the brain with heated blood or saline solution also gives rise to increased respiratory activity The respirations in the chill phase usually are more shallow thar

severe chill reaction removes the factor which maintains the blood pressure in the chill phase and a very severe fall in arterial pressure may occur in such patients In most instances however the effects of accelerated blood flow make themselves felt and the arterial pressure returns toward normal The flow through the skin is greatly increased and accordingly the blood from an antecubital vein may exhibit an arterial level of oxygen saturation This finding indicates that the arteriovenous shunts in the cutaneous circulation open so that the venous blood is arterialized The arm to tongue circulation time is accelerated and the cardiac output may be two or more times as great as the control value It is apparent that maintenance of cardiac work at this high level for some time may result in the development of congestive failure in elderly debilitated or cardiac patients The renal blood flow is greater than normal in the flush phase and diuresis may occur unless the patient has become dehydrated The urine formed usually is alkaline

Defervescence is not sharply delimited from the flush phase but consists in a gradual return of all the functions toward normal It is initiated by a lowering in heat production of unknown origin

It is evident from all of the above discussion that a phenomenon of such common occurrence as fever is actually a complicated physiological process which influences cardiovascular renal and respiratory function variously depending upon the stage of the febrile reaction encountered

Thyroid Disease —The flush which characterizes thyrotoxicosis is well known and is obviously a mechanism for the dissipation of the excessive heat produced by the body and accordingly fever consequent solely to thyrotoxicosis is rare Microscopic examination of the capillaries of the nailbed or other parts of the skin in patients with Graves disease reveals widespread vasodilatation There is therefore an increased amount of blood in the skin at any given moment so that a larger than normal volume of blood is being cooled at one time the small increase in total circulating blood volume which has been found to occur in thyrotoxicosis possibly is a reflection of this phenomenon Not only is the amount of blood present in the skin increased in amount but the volume flowing through the cutaneous vessels each minute is also considerably increased Measurements of the output of the heart in thyrotoxicosis show a rough parallelism with the increase in metabolism a slight tendency toward a greater increase in the former than the latter has been found at high levels of metabolism Studies of cutaneous flow on the other hand show a considerably greater increase in the circulation through the skin than in that of the body as a whole It is apparent that the increased blood content and circulatory volume of the skin provide an effective cooling mechanism The fact that these mechanisms are called into play at ordinary temperatures explains the intolerance to heat which occurs in

cardiac output and venous pressures fall and vasoconstriction though maximal or close to it is inadequate to maintain arterial pressure so that the latter falls This state characterized by low arterial and venous blood pressures greatly reduced cardiac output and slowed circulation time and markedly diminished venous blood oxygen content is indistinguishable from surgical shock except for several facts i e (1) the rectal temperature is high rather than low, (2) the blood volume is normal (3) there is no profound decrease in oxidations with diminution of oxygen consumption and (4) the state usually is reversible and self limited Another interesting phenomenon associated with the vasoconstriction of the chill phase is the fading or non appearance of erythematous rashes peculiar to the disease causing the fever so that a diagnostic aid thereby is lost temporarily Termination of the chill phase results in the appearance of the rash, however

The onset of the *flush phase* is associated with a sudden intense vasodilatation which can be seen clearly on examination of the capillaries of the nailfold and which results in the characteristic reddening of the skin In some instances alternate dilatation and constriction may be seen for a few minutes and then the intense lasting dilatation develops The nature of the mechanism involved is not established but it appears that the steadily rising temperature of the blood finally reaches a point at which sympathetic vasodilator impulses are discharged from the hypothalamus It is of interest that gooseflesh may occur again at this point The sudden gush of heated blood into the skin rapidly elevates the cutaneous temperature and a point is soon reached i e 33 to 35 C, when reflexes are initiated which give rise to a generalized drenching sweat Vasodilatation and sweating accelerate heat dispersal so that little or no further rise in rectal temperature occurs and a plateau appears in the temperature curve

The flush phase like the chill, is characterized by abnormally increased respiratory activity, but in some instances it is less marked during the former than the latter The respiratory rate usually decreases somewhat during the flush phase and the tidal air volume is larger Nevertheless hyperventilation still is present and the decreases in alveolar air and blood carbon dioxide contents described above persist as does also alkalosis In the case of fevers physically induced the cooling effects of the evaporation of sweat are prevented by an environment saturated with water vapor so that hyperventilation and alkalosis are more severe and sweat production sufficiently increased to result in dehydration in the course of only a few hours

The circulatory dynamics of the flush phase are as equally characteristic as those of the chill phase The sudden vasodilatation often results in a fall in arterial blood pressure, the onset of the flush phase in a patient experiencing a

and the rectal temperature rises even though the skin temperature is lower than normal

Anemia — The effects of anemia on the cardiac output are similar to those caused by breathing air containing low concentrations of oxygen both cause an increase in the output of the heart and flow of blood presumably to counteract the effects of tissue anoxia However in both conditions the increased flow of blood is not distributed uniformly throughout the body The flow through the skin particularly that of the hands and feet may increase only slightly or may actually be diminished *The mechanisms which cause this cutaneous vasoconstriction* are not known except that sympathetic nervous system activity must be involved *The result is a shunting of blood away from the skin and to the* vital internal organs This change is of little clinical importance but it is interesting in that it explains the complaint of cold hands and feet commonly encountered in patients with anemia In a patient with severe anemia the vasoconstriction in the vessels of the skin may be so severe and so widespread as to result in a rise in rectal temperature This phenomenon probably is responsible for the unexplained low grade fevers often seen in patients with severe anemia a feature frequently present in pernicious anemia promptly to disappear when with liver therapy the blood count rises

Emotional States — Almost all patients admitted to a hospital are found to have a small but definite elevation in rectal temperature on the day of admission Studies of the effects of emotion on circulation through the skin have shown that fear anxiety etc give rise to intense cutaneous vasoconstriction Such vasoconstriction could cause easily the rise in rectal temperature seen in otherwise afebrile patients on admission to the hospital In its more persistent form this vasoconstriction could give rise to the cold clammy hands and feet seen in nervous individuals

Vagal Activity in Heart Disease

Many of the manifestations of cardiovascular disease become intelligible only in the light of recent studies which demonstrate or suggest the role of vagal hyperactivity in these phenomena

Carotid Sinus Hypersensitivity — *The syncopal syndromes which result* when a hypersensitive carotid sinus in man is stimulated have been studied extensively They fall into three main groups (1) marked slowing of the heart rate to 50 or less per minute sometimes associated with partial heart block (2) a striking fall in blood pressure and (3) syncope apparently consequent solely to diminished cerebral flow Hypersensitivity of the carotid sinus develops in many elderly arteriosclerotic individuals but only uncommonly in a degree

this disease additional vasodilatation and increase in cutaneous flow cannot occur or at least are limited The fact that these mechanisms for heat dispersal already are partially or maximally active leads to unusually high degrees of fever when patients with Graves disease develop infections

Physiological studies of the circulation in myxedema show quite the reverse In this disease a low metabolic rate might result in a fall in body temperature if it were not for compensatory changes in cardiovascular dynamics Cutaneous vasoconstriction is readily demonstrable by study of the capillaries of the skin in patients with myxedema this vasoconstriction contributes to the pallor which is characteristic of hypothyroidism Measurements of cardiac output show a decrease in that function which is greater than the diminution in metabolic rate Also the flow through the skin is lowered more markedly than that through the body as a whole The importance of these changes in securing a conservation of body heat is clear In addition these phenomena explain in part the intolerance to exposure to cold which is characteristic of myxedema The normal cutaneous response to exposure to cold is vasoconstriction but this cannot occur in patients with myxedema since the vessels of the skin already are markedly constricted

Chronic Cardiac Decompensation —The importance of cutaneous blood flow in the genesis of the dyspnea of chronic congestive failure is not widely appreciated Clinical observation has shown, however that patients with this disease may be extremely uncomfortable in a stuffy room or when covered with heavy blankets and may experience partial relief of their dyspnea on exposure to cool air In passing it might be pointed out that some of the favorable effect which an oxygen tent may have on patients with severe congestive failure probably is consequent to the fact that the air in such a tent has been passed over ice The mechanisms involved in the relation between dyspnea and external temperature have been fairly well elucidated The dispersal through the skin of four fifths of the heat lost by the body depends on a normal cutaneous blood flow It has been shown, for instance that the application of tourniquets to all four extremities in man so impairs the dispersal of heat as to give rise to an elevation in rectal temperature When heat dispersal through the skin is diminished other mechanisms become hyperactive One such mechanism is sweating and another is hyperpnea The panting of the dog on a hot day is a familiar phenomenon which has a parallel in the exacerbation of dyspnea in cardiac patients when exposed to heat Measurements made in patients with congestive failure show that they depend on the lungs for about 50 per cent more heat dispersal than normal Since anything which increases respiratory activity favors dyspnea it is clear that exposure to heat must do likewise In many instances the increased respiratory activity, which occurs is inadequate to compensate for poor cutaneous flow,

tated in such a case Application of cold to this small area of the skin results in no detectable change in pulse blood pressure or blood flow, and accordingly cardiac work is not increased Previous novocaine block of the sensory nerves *from the cold area prevents the effect of exposure to cold in the precipitation of angina but a tourniquet about the arm does not* It is clear, therefore that exposure of the skin to cold activates a reflex arch which favors the occurrence of angina presumably by causing coronary spasm through vagal activity Other reflexes which apparently also result in coronary spasm may arise in the viscera Thus a number of instances in which angina was relieved by operative removal of a diseased gall bladder have been described In addition overdistention of *the stomach by a large meal may in suitable subjects give rise to anginal attacks long before the effect on the circulation of digestion and absorption of the food* can occur These two phenomena precipitation of angina by exertion in the cold or after a heavy meal are quite common and accordingly well known to clinicians It is possible that the angina which may occur in patients with coronary sclerosis as a consequence of emotional upset also may represent the result of coronary constriction secondary to vagal hyperactivity In treating cardiac patients it must be borne in mind that digitalis a drug with strong vagal effects *may exacerbate angina pectoris whereas quinidine which inhibits the action of* the cardiac vagal fibres may cause improvement

Partial Heart Block — Partial heart block as manifested by prolonged P R interval is of common occurrence in patients with acute rheumatic fever and in coronary artery disease In some instances the cause of this type of block is an anatomical lesion but in many it appears to be functional Thus almost all pa*tients who have a prolonged P R interval during the course of rheumatic fever* and many who exhibit it as a manifestation of myocardial infarction show shortening of the P R interval to normal after the administration of atropine A similar finding was noted in the case of a patient with a prolonged P R interval associated only with a large intra auricular septal defect (proven by autopsy) The origin of the vagal impulses causing this functional type of partial heart block is obscure *but it is known from work done in animals that reflexes which affect the heart through the vagus nerve may arise in the root of the aorta the auricles the great* veins and the pulmonary arteries All of these may become inflamed during an attack of rheumatic fever In addition the aorta may be involved severely in an arteriosclerotic process Pulmonary congestion consequent to congestive failure may so raise the pulmonary vascular pressure as to activate vagal reflexes acting on the heart In addition anoxia such as that caused by congenital heart disease *with a shunt or by severe congestive failure may result also in a vagal* discharge

In occasional instances severe emotional strain may give rise to partial heart

severe enough to cause symptoms The afferent fibres, which carry the impulses from the sensitive carotid sinus run through the glosso pharyngeal nerve whereas the efferent impulses, which act on the heart are vagal Consequently factors, which influence vagal tone or activity also affect the sensitive carotid sinus Thus digitalis, which is known to increase vagal tone tends to increase sensitivity of the carotid sinus Contrariwise drugs which inhibit the vagus may interrupt the reflex arc which when activated gives rise to the syndrome of carotid sinus syncope or convulsions substances which increase sympathetic tone may counter act the effects of vagal activity These facts are used in the treatment of the syndrome by the administration of atropine or such sympathomimetic amines as ephedrine or epinephrin

Vagovagal Syndromes —An uncommon but interesting syndrome is one which has been named vagovagal because a reflex arc consisting of both afferent and efferent vagal fibres is involved in the disorder The symptoms consist of syncopal attacks or convulsive seizures associated with and following the act of swallowing It may be reproduced in some patients who exhibit these phenomena spontaneously by inflating a balloon in the esophagus or the stomach The fragmentary physiological studies available indicate that this syndrome closely resembles that associated with hypersensitivity of the carotid sinus except that both afferent and efferent pathways are in the vagus nerve As in the case of carotid sinus hypersensitivity the vagovagal syndrome may be treated successfully by means of atropine or ephedrine

Fainting Spells —A few studies of the changes in the circulation during the course of an ordinary fainting spell consequent to emotion or to pain suggest that this too is a vagal syndrome as indicated by marked bradycardia and hypotension

Angina Pectoris —The basis for the occurrence of anginal pain is generally considered to be a disproportion between the needs of the myocardium for blood and the supply available to the cardiac muscle through narrowed sclerotic arteries Nevertheless it is known that a diseased artery is more likely to go into spasm than a normal one accordingly it is not surprising that recurrent spasm is also a factor in precipitating attacks of angina pectoris In some instances such spasm can be shown to be reflex in origin The vagus nerve endings in the myocardial vessels have a vasoconstrictor action so that reflexes causing coronary arterial spasm must act through the vagus nerve A number of clinical applications of this fact have been demonstrated It has long been known that exposure to cold increases the frequency of attacks of angina pectoris in patients with the syndrome but only recently has the reflex nature of this effect been shown Recent studies have demonstrated that the application of ice to one finger in a patient with angina increases the ease with which attacks of pain may be precipi

tated in such a case. Application of cold to this small area of the skin results in no detectable change in pulse, blood pressure or blood flow, and accordingly cardiac work is not increased. Previous novocaine block of the sensory nerves *from the cold area prevents the effect of exposure to cold in the precipitation of* angina but a tourniquet about the arm does not. It is clear, therefore, that exposure of the skin to cold activates a reflex arch which favors the occurrence of angina presumably by causing coronary spasm through vagal activity. Other *reflexes which apparently also result in coronary spasm may arise in the viscera.* Thus a number of instances in which angina was relieved by operative removal of a diseased gall bladder have been described. In addition, overdistention of the stomach by a large meal may, in suitable subjects, give rise to anginal attacks long before the effect on the circulation of digestion and absorption of the food can occur. These two phenomena, precipitation of angina by exertion in the cold or after a heavy meal, are quite common and accordingly well known to clinicians. *It is possible that the angina which may occur in patients with coronary* sclerosis as a consequence of emotional upset also may represent the result of coronary constriction secondary to vagal hyperactivity. In treating cardiac patients it must be borne in mind that digitalis, a drug with strong vagal effects, *may exacerbate angina pectoris, whereas quinidine, which inhibits the action of* the cardiac vagal fibres, may cause improvement.

Partial Heart Block. — Partial heart block, as manifested by prolonged P R interval, is of common occurrence in patients with acute rheumatic fever and in coronary artery disease. In some instances the cause of this type of block is an anatomical lesion, but in many it appears to be functional. Thus almost all patients who have a prolonged P R interval during the course of rheumatic fever and *many who exhibit it as a manifestation of myocardial infarction show shortening* of the P R interval to normal after the administration of atropine. A similar finding was noted in the case of a patient with a prolonged P R interval associated only with a large intra auricular septal defect (proven by autopsy). The origin of the vagal impulses causing this functional type of partial heart block is obscure, but it is known from work done in animals that reflexes which affect the heart through the vagus nerve may arise in the root of the aorta, the auricles, the great *veins and the pulmonary arteries. All of these may become inflamed during an* attack of rheumatic fever. In addition the aorta may be involved severely in an arteriosclerotic process. Pulmonary congestion consequent to congestive failure may so raise the pulmonary vascular pressure as to activate vagal reflexes acting on the heart. In addition, anoxia such as that caused by congenital heart disease with a shunt or by severe congestive failure may result also in a vagal discharge.

In occasional instances severe emotional strain may give rise to partial heart

block with prolonged P R interval and dropped beats This is apparently vagal in origin for in one such patient who exhibited heart block recurrently in association with severe emotional upsets the administration of atropine was followed by the prompt return of the electrocardiogram to normal

Patients who have higher degrees of block may show frequent fluctuations in block which do not appear to be due in all cases to changes in the severity of an organic lesion this type of phenomenon also may be vagal in origin When it occurs it may be associated with recurrent Stokes Adams attacks which occasionally can be aborted by changing the partial to complete block this may be accomplished by the use of large doses of digitalis

Auricular Fibrillation — Stimulation of the vagus nerve has been shown in a large number of experiments to give rise to auricular fibrillation in a variety of laboratory animals In addition the injection intravenously of acetyl choline or of its derivative acetyl B methyl choline chloride has resulted in transitory auricular fibrillation in some normal men and in a proportion of intact unanesthetized dogs Early studies of the nature of auricular fibrillation showed it to be a consequence of circus movement in the auricular myocardium circus movement is favored by anything which either (1) shortens the refractory period or (2) slows conduction in the auricular muscle Shortening of the refractory period has been demonstrated to be a consequence of the action of the vagus nerve on auricular muscle Clinically the role of the vagus in auricular fibrillation has been studied in a number of conditions For example all of a reported series of patients with Graves disease and regular cardiac rhythm developed auricular fibrillation after the injection subcutaneously of mecholyl in moderate dosage In the case of patients with auricular fibrillation associated with rheumatic heart disease or with myocardial infarction an unusually high incidence of auricular fibrillation was noted among patients who had at some time or other exhibited evidence of increased vagal tone in the form of partial heart block or sinus bradycardia The source of the vagal impulses affecting the heart in patients with cardiac disease is not clear but as pointed out above in the discussion of partial heart block many of the thoracic viscera may be involved The question naturally arises as to why atropine does not cure auricular fibrillation the answer lies in the fact that so large a dose of atropine is required for complete paralysis of the cardiac vagus as to make its clinical use impossible It should be borne in mind however that the favorable effect of quinidine may be due in some measure to its action in depressing the cardiac vagus

Dyspnea —The changes in blood gases circulation rate and volume and pulmonary dynamics which favor the occurrence of dyspnea in chronic congestive failure, have been described by many authors The role of reflex factors operating through the vagus nerve in the genesis of dyspnea or hyperpnea is a real

one although its relative importance cannot be evaluated Reflexes of two types both of which originate in congested lungs may give rise to hyperpnea In one type of reflex first described by Churchill and Cope simple distention of the vascular bed of the lungs results in rapid shallow respiration In another type the effect of pulmonary congestion in increasing the rigidity of the lungs stimulates nerve endings in the parenchyma and thereby activates a reflex i e the Hering Breuer reflex which gives rise to dyspnea It is possible that the favorable effect of morphia on cardiac dyspnea represents a depression of these reflex mechanisms

Cardiac Asthma — The cause of wheezing respiration and musical rales which may be noted during acute episodes of cardiac dyspnea or at times in chronic cardiac dyspnea is obscure but available evidence implicates the effects of vagal activity on the bronchial musculature Injection of novocaine into the neck about the vagus nerve results in disappearance of the musical rales on that side The origins of the impulses which give rise to stimulation of the bronchial endings of the vagus nerve are not known Here again it is not unlikely that the favorable effect of morphia on this manifestation of heart disease is due to depression of the reflex mechanism involved

Pulmonary Edema — Almost a century ago the first reports were published of the occurrence of pulmonary edema in animals following section of the vagi and these observations have been confirmed amply since that time Indeed aside from pulmonary edema induced in animals by anoxia by inhalation of toxic gases and only in rabbits by injection of epinephrin this is the only type of pulmonary edema which can be caused to occur experimentally with regularity Amplification of these studies has been affected by observations made after novocainization of the lung root It has been reported that the occurrence of this type of experimental pulmonary edema is preceded by marked vasodilatation and congestion so that it is felt that pulmonary edema of this type is consequent to some neurogenic change in vasomotor control and in capillary permeability These observations have been applied in the explanation of pulmonary edema which may occur in patients with cerebral trauma with cerebral vascular accidents or with inflammatory disease of the central nervous system The relation of the above mentioned studies in animals to the acute pulmonary edema which often occurs in patients with heart disease is far from established On the other hand the concept widely accepted by clinicians which states that pulmonary edema in cardiacs is consequent to acute failure of the left ventricle is regarded as highly improbable by physiologists It is pertinent in this regard that the single most effective therapeutic measure in pulmonary edema is the injection of morphia

Action of Digitalis — The vagal action of digitalis is well marked and is im

portant therapeutically as well as toxicologically Thus its action in slowing the heart rate so remarkably in auricular fibrillation is evidence of a vagal effect on the auriculoventricular node which is useful it is largely counteracted by atropine This action on the a v node is made use of also in converting partial to complete heart block On the other hand the vagal effect of digitalis on the auricle itself is to increase the tendency toward circus movement which may or may not be beneficial It is definitely useful in converting auricular flutter to fibrillation it is neither helpful nor harmful when it accelerates the rate of circus movement in auricular fibrillation and in rare instances it may be undesirable when it converts sinus rhythms to auricular fibrillation The effects of the vagal action of digitalis in angina pectoris and in carotid sinus hypersensitivity have been discussed already The toxic effects of digitalis overdosage are to some extent modified favorably by the administration of atropine

Some Effects of Acidosis

Fixed Acidosis — The part played by blood alkali in the transport of carbon dioxide is well known only small amounts of carbon dioxide exist in the blood as carbonic acid the rest being combined with base in the form of bicarbonate The ratio of carbonic acid to bicarbonate determines the pH of the blood and accordingly changes in bicarbonate must be paralleled by corresponding changes in free carbonic acid level if the hydrogen ion concentration is to remain within the normal range While the regulation of the excretion of base and of fixed acids is a renal function control of the level of blood carbonic acid is effected by changes in respiratory dynamics Thus acidosis consequent either to accumulation of fixed acids or to the loss of base so diminishes the amount of alkali available for the formation of bicarbonate as to require that the free carbonic acid likewise decrease Accordingly increased respiratory minute volume affected chiefly by increased tidal air volume occurs and carbon dioxide is blown off The blood pH is maintained at a normal level in this manner This type of respiration i e Kussmaul breathing is recognized as a manifestation of acidosis although it should be pointed out that striking increases in respiratory activity do not occur unless acidosis is at least moderately severe

Although the effects of increased respiration in acidosis in preventing a change in the pH of the blood have been widely emphasized certain other phenomena are also important The formation of carbon dioxide in the tissues goes on at the normal rate in acidosis Accordingly a marked lowering of carbon dioxide carrying capacity of the blood might result in accumulation of carbon dioxide in the tissues unless a compensatory increase in blood flow occurred Experiments in animals have shown that acidosis with its lowered blood carbon

dioxide capacity is associated with *an increase in cardiac minute volume output* much as anemia with its lowered blood oxygen capacity causes an elevated cardiac output This persistent increase in cardiac work in acidosis may result ultimately in *myocardial failure particularly if the heart already is itself poisoned by* acidosis weakened by organic disease or strained by hypertension such as occurs in nephritis The almost uniform occurrence of congestive heart failure late in the course of uremic acidosis is well known

The above described changes in respiratory and cardiovascular function explain in part the lessened capacity for work exhibited by patients with acidosis *Increased respiratory and cardiac minute volume at rest leave a decreased reserve* for the demands of work so that dyspnea and weakness develop at a lower level of activity than normal even in the absence of myocardial weakness and pulmonary congestion and edema *Another factor of at least equal importance in* this connection is the change in the blood itself for the lowered alkali reserve makes less base available for combination with the lactic acid produced during exercise and acidosis is therefore associated with inability to build up a normal oxygen debt The development of myocardial insufficiency and pulmonary edema greatly aggravates the tendency toward the occurrence of dyspnea and weakness

The action of acidosis in causing strain on the heart and the lessened ability to develop an oxygen debt in acidosis are of some interest in regard to the treatment of congestive failure Acidifying salts usually ammonium chloride may *be used in the treatment of edematous cardiacs* if given in doses of 10 grams a day or more they may although favorably affecting the edema decrease ability to perform work

Gastric *function also is altered by the occurrence of acidosis* The formation *of hydrochloric acid in the stomach decreases as the blood bicarbonate fails* ceasing entirely when the latter reaches approximately 30 volumes per cent It is probable that achlorhydria so induced may be responsible for some of the gastrointestinal *symptoms of acidosis and may favor the development of the iron and* protein deficiencies seen particularly in chronic uremic acidosis

Carbon Dioxide Acidosis — The chronic accumulation of excessive amounts of carbon dioxide in the blood occurs only in patients with severe pulmonary disease such as marked emphysema severe persistent asthma or extensive fibrosis of whatever etiology

Changes in the electrolyte pattern of the blood become apparent as soon as *retention of carbon dioxide is detectable The increase in carbon dioxid tends* to increase the ratio of carbonic acid to bicarbonate thereby leading to an increase in hydrogen ion concentration However a compensatory increase in bicarbonate *often considerable* occurs consequent to retention of base and also

to loss of chloride the ratio of carbonic acid to bicarbonate is unchanged and the blood pH usually lie in the normal range The finding of a disturbed electrolyte pattern i e elevated blood bicarbonate and lowered chloride, indicates that carbon dioxide retention has occurred in patients with pulmonary disease It has been known for years that such patients do not show the expected degree of hyperpnea and when given air enriched with carbon dioxide to breathe exhibit a remarkable tolerance for that gas Increased blood carbon dioxide combining power makes these phenomena possible

Although the consequences of carbon dioxide retention in respect to respiration are largely counteracted by the above described mechanism in patients with chronic pulmonary disease there is another effect which is apparent and is of some clinical interest Carbon dioxide is a capillary vasodilator, and patients with carbon dioxide retention therefore present an appearance of plethora which exceeds often to a considerable degree that which is expected from a given red blood cell count

The gastrointestinal manifestations of chronic pulmonary disease are well known and are ascribed correctly to the anoxia which commonly occurs in that condition However it is possible that another factor is contributory The secretion of acid by the stomach parallels as pointed out above the level of blood bicarbonate Patients who exhibit the changed electrolyte pattern of carbon dioxide retention should have also hyperchlorhydria

Pathological Physiology of Some Common General Symptoms

Attempts to elucidate the mechanisms underlying many of the common complaints associated with illness generally are unsatisfactory since these subjective manifestations of disease may have no objective counterpart Thus while some idea of the severity of the symptom of anorexia may be obtained by calculating a patient s caloric intake such feelings as those of fatigue and weakness may be gauged only by the patient s own estimate of the severity of the symptom Accordingly it is clear that severity of some symptoms will depend upon such factors as the patient s reaction to discomfort whether or not he is introspective, what his mood is at the time and whether or not there is any impairment of sensation or consciousness In some circumstances the evaluation of vague general symptoms may be largely a matter of semantics the same words may have widely divergent meanings to different individuals

Anorexia —Loss of appetite occurs in a wide variety of disorders and no physiological change common to all has been demonstrated as its cause

The importance of the cerebral cortex in the genesis of this symptom is well established Cortical function may depress appetite in various ways (1) through

conscious or unconscious fear that eating may precipitate pain nausea or vomiting as in some patients with organic gastric disease ( ) through feelings of disgust as when an individual who had never previously seen a raw oyster first attempts to engage it on his fork (3) in association with acute feelings of fear rage anxiety etc (4) through more complex mechanisms such as appear to be involved in severe neuroses including anorexia nervosa In some of the above particularly the anorexia associated with disgust anxiety fear rage etc motor changes presumably occur in the stomach for vomiting may ensue Available evidence suggests delayed gastric emptying time and depressed peristalsis in some individuals with anorexia which occurs as a consequence of the activity of psychic factors Vasomotor changes in the gastric mucosa which may result in depressed secretion may occur also

Organic disease of the gastrointestinal tract very commonly is associated with anorexia the organic lesion giving rise to this symptom may be in the stomach or remote from it In some conditions such as pyloric obstruction delayed emptying time of the stomach may be a factor responsible for anorexia Depressed gastric motility consequent either to local or to reflex factors may be important in other conditions The relation of depressed secretory activity of the stomach to loss of appetite is not established but may be significant in some forms of gastritis

A large number of systemic diseases give rise to anorexia and also to delayed gastric emptying and depressed peristalsis These may be classified under several heads (1) anoxic states such as cardiac decompensation severe pulmonary disease severe anemia and cirrhosis in the last named stasis giving rise to anoxia is limited to the portal circulation (2) edematous states such as cardiac decompensation nephritis and hypoproteinemia due to starvation or hepatic or renal disease (3) febrile illnesses The association of loss of appetite and depressed gastric motor function is striking in all of these disorders Nevertheless the role of impaired secretion must be considered also In fevers and in acidosis the secretion of hydrochloric acid in the stomach is greatly diminished or even absent apparently as a consequence of lowering of blood bicarbonate levels

A variety of metabolic disorders may give rise to anorexia Patients with myxedema and with Simmonds cachexia eat poorly Whether this reflects in some manner the low metabolic requirements of these patients is not clear On the other hand in both of these diseases sluggish gastrointestinal motility occurs Metabolic disorders giving rise to acidosis such as uremia untreated severe diabete etc may be associated with profound anorexia As pointed out previously secretion of gastric hydrochloric acid is depressed in these conditions Recent studies have shown that following a variety of traumata a condition develops which has been given the ambiguous name of alarm reaction This will be

discussed more fully later in this chapter at this point it will be pointed out only that profound anorexia whose mechanisms are completely unknown, occurs in individuals manifesting this reaction The association of hypoglycemia with increased appetite has led to attempts to relate anorexia to hyperglycemia The latter concept has little to support it for in diabetes there may be marked hyperglycemia associated with ravenous hunger Other common causes for anorexia are inactivity and thiamin deficiency their mechanisms are not known

It is clear from all of the above discussion that data bearing on the pathogenesis of anorexia are too fragmentary to permit of generalizations Nevertheless the role of delayed gastric emptying and depressed peristalsis seems to be important in many diseases which give rise to loss of appetite, decreased secretion of gastric hydrochloric acid may possibly be a factor also

Loss of Weight —The occurrence of loss of weight is consequent to the establishment of a negative caloric balance The latter in turn is a function of several factors (1) decreased intake (2) increased metabolism (3) inadequate digestion and absorption and (4) impaired utilization The first has been discussed already In considering the second it is important to bear in mind that calculations of caloric requirements must be based on total daily metabolism rather than basal metabolism Thus a normal individual doing very heavy manual labor for 10 hours a day may have a greater caloric requirement per day than a patient with thyrotoxicosis of the same age height weight and sex but who is at rest in bed The occurrence of increased metabolic rates in fever thyrotoxicosis acromegaly leukemia lymphoma and polycythemia vera requires no comment here Defective digestion and absorption such as occurs in patients with extensive disease of the gastrointestinal tract diarrhea short circuits in the intestinal tract pancreatic insufficiency sprue etc are self evident causes of weight loss Impaired utilization of carbohydrate occurs in diabetes and in thiamin deficiency both of which may be associated with profound weight loss In patients with the alarm reaction following trauma burns and vascular accidents a catabolic state develops which is not amenable to any known treatment Hyperglycemia and glycosuria and a negative nitrogen balance occur In association with loss of weight are negative potassium and often phosphate balances and creatinuria The mechanisms underlying this state are not understood it has been suggested that a deficiency of adrenal cortical steroids which have anabolic functions may be responsible

Cachexia —The term cachexia has been in the medical literature since the time of the earliest Greeks For centuries cachexia was considered a specific disease or at least syndrome Actually however the term merely means "bad condition" Patients characterized as cachetic exhibit marked loss of flesh and in addition certain other features formerly regarded as specific These include

an inelastic and sallow or pigmented skin and a pinched or depressed expression It appears that cachexia is therefore loss of weight together with a variable amount of anemia dehydration and pigmentation due to vitamin deficiencies or other factors The term cachexia should not be used in any specific sense

Weakness — Discussion of the complaint of weakness is difficult because of the many meanings the word may have The patient with angina who complains of a feeling of weakness in his chest the neurotic who feels weak in the stomach and the patient with a hemiparesis who feels weak in one arm and leg are all using the term to express different sensations In addition weakness must be differentiated in some instances from easy fatiguability and from partial loss of ability to perform complex coordinated movements This discussion will be limited to a consideration of muscular weakness

Muscular weakness may exist as a consequence of a disorder of the nervous system of the muscle itself and of the neuromuscular junction The occurrence of creatinuria in association with weakness is well known In some instances overt creatinuria may be absent but impairment of creatin utilization can be demonstrated by suitable tolerance tests Impaired utilization of creatin with or without creatinuria occurs in muscular dystrophies fevers chronic cardiac decompensation myxedema thyrotoxicosis and alarm reactions associated with trauma burns vascular accidents etc In all of these disorders and often for many weeks after apparent recovery from them muscular weakness may be a prominent complaint The various conditions listed above appear to distort the function of certain intracellular enzyme systems in muscle in ways not completely understood

The importance of acetylcholine in neuromuscular function is well established Conditions for its synthesis are not well known except that oxygen is necessary Recent studies suggest that high concentrations of pyruvate depress the synthesis of acetylcholine Diseases in which are found elevated blood pyruvate levels include anoxia congestive failure fever thiamin deficiency and the alarm reaction which follows trauma burns and vascular accidents The origin of increased blood pyruvate levels may be either (1) decreased utilization of pyruvate as in anoxia congestive failure and thiamine deficiency or ( ) increased formation of pyruvate from stored carbohydrate or alanine as in fever and the catabolic state known as the alarm reaction

A specific relationship between blood potassium and muscular weakness appears to exist in familial periodic paralysis On the other hand in chronic adrenal insufficiency the blood potassium may be elevated in spite of which weakness may be severe

It should not be concluded that the above discussed biochemical phenomena are sufficient in themselves to account for all types of muscular weakness en

countered in clinical medicine The loss of substance from the nervous system or from the muscles themselves derangements of the skeletal system or the attachments of muscles and many other mechanical factors must operate also

Malaise — A term commonly used in describing some of the vague complaints associated with infectious or febrile states is malaise It may connote weakness fatigue depression aches and pains irritability or almost anything else that a sick patient may experience Restriction of the use of the term to infectious processes appears to be unreasonable for patients with a variety of acute organic non febrile diseases or with emotional disturbances may have precisely the same complaints Indeed as the word implies, the term was meant to signify ill ease which under different circumstances can have a wide variety of meanings Since it has no specific connotation its value is doubtful There are no abnormalities in any physiological or chemical measurement that can be correlated with it

Fever — Mention has already been made of the cardiovascular and respiratory changes which occur during fever The fundamental mechanisms causing fever are not established but certain facts are known Under ordinary circumstances the body maintains a normal temperature in spite of changes in environmental temperature as with the seasons or in heat production as with mild exercise utilization of food thyrotoxicosis or myxedema If the brain in animals is sectioned below the hypothalamus a state of poikilothermia results in which the temperature of the organism becomes that of the environment section of the brain above the hypothalamus does not have this effect Localized destruction of the hypothalamus also makes animals lose their normal responses to changes in body temperature The mechanisms making for dissipation of body heat are cutaneous vasodilatation sweating and hyperventilation Those which result in conservation of heat are cutaneous vasoconstriction and shivering

Fever implies a lack of balance between heat formation and heat dispersal Some of the circumstances which give rise to fever are readily understandable Remaining in a hot environment or immersing oneself for any length of time in a hot bath must, necessarily give rise to impaired heat dispersal and thereby cause fever The loss of ability to sweat either congenital as in anhidrotic ectodermal dysplasia or acquired as after residence in hot desert areas obviously favors the development of fever Marked elevations of heat production as in the case of severe exercise does likewise The problem of endogenous fever i e that associated with infection or with tissue breakdown is still a puzzling one A prodromal period is characteristic for this type of fever its mechanism is quite unknown The development of fever is accompanied by a moderate increase in heat production which in the case of febrile illnesses is not associated with activation of heat dissipating mechanisms in a normal manner Thus in the period dur

ing which fever is developing instead of vasodilatation and sweating the patient exhibits cutaneous vasoconstriction and little sweating Indeed shivering may occur at body temperatures well above normal Endogenous fever therefore is associated with a resetting of the hypothalamic thermostatic controls at a level higher than normal The factors that cause this change and determine the level at which it occurs and its duration are entirely unknown This resetting of thermostatic control is more than a theoretical concept for strong evidence that it occurs is afforded by the course of patients with lesions in or trauma to the hypothalamus Such individuals usually show extreme hyperthermia some may exhibit marked hypothermia The only explanation for these manifestations is a resetting of the level of body temperature at which thermostasis is maintained

Pathological Physiology in Diagnosis

A large number of tests based on knowledge of the physiology of disease have been devised as aids in diagnosis Each has been described and evaluated somewhere in this group of volumes in connection with the disease in which it may be used diagnostically and consequently *no attempt will be made to present a* similar analysis here

It should be emphasized that on many occasions the laboratory is a hindrance rather than an aid in diagnosis The reasons for this may be classified under two main heads (1) the use of tests in an attempt to compensate for incomplete or poorly performed history taking and physical examination (2) incomplete knowledge as to the significance of the findings of tests The first of these requires no comment except strong condemnation The lazy or incompetent physician is not likely to be helped by laboratory tests and may be hindered There are hundreds of tests which can be done in man and the choice of the test likely to be helpful depends upon a well rounded knowledge of disease Reliance on the result of a laboratory test to the exclusion of clinical data commonly leads to error Thus every patient with a positive Widal test does not have typhoid fever nor every patient with glycosuria pancreatic diabetes The interpretation of a test as common as the blood non protein nitrogen determination cannot be made without accurate knowledge of the patient s clinical status for elevation of the non protein nitrogen level in the blood may be the consequence of dehydration shock chronic congestive failure massive hemorrhage into the gastrointestinal tract or prostatic obstruction one cannot make a diagnosis of nephritis on the basis of the blood chemical findings alone Similarly albuminuria may have a number of extra renal causes including fever congestive failure and the administration of such vasoconstrictor substance as ephedrin or epinephrin It is particularly in the field of cardiovascular disease that physiological tests are misin

terpreted most often because of lack of understanding of their significance While it is true that slowed circulation time increased venous pressure and lowered vital capacity are characteristic of cardiac decompensation, it must be borne in mind that these deviations from the normal occur in other conditions Slowed circulation times are found also in myxedema polycythemia vera, shock, some instances of mediastinal tumor and in normal subjects whose skin is exposed to cold High venous pressures occur with severe emphysema, some mediastinal tumors pleural effusion extreme degrees of pneumothorax and arteriovenous aneurysm Low vital capacity occurs in severe emphysema, intrathoracic tumor pneumothorax pleural effusion and obesity Contrariwise congestive failure may occur in the presence of normal circulation times when fever, thyrotoxicosis anemia and possibly beriberi are present also Also a venous pressure within normal limits is often found in patients with other manifestations of myocardial insufficiency It is clear that these tests may be misleading in diagnosis unless their significance is understood A factor which makes for difficulty in interpretation at times is the wide normal range which is characteristic of physiological measurements That the normal basal metabolic rate lies between plus or minus 10 to 15 per cent is overlooked occasionally Similarly a circulation time of 13 seconds may be difficult to reconcile with thyrotoxicosis unless it is realized that the normal range is 12 to 19 seconds by most methods and that if a patient starts at the latter figure an acceleration of six seconds though definitely significant would not remove his circulation time from the overall normal range

All of the above considerations emphasize the need for accurate clinical appraisal in conjunction with evaluation of the results of diagnostic tests, the latter cannot replace the former

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CHAPTER II

INFECTIOUS DISEASES OF BACTERIAL ORIGIN

By HUGH K. WARD

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INTRODUCTION

The curriculum of every medical student contains a course which is labelled bacteriology. The student should be grateful that in very few instances is the threat carried out, perhaps because bacteriologists are essentially a kindly race, perhaps because they themselves have not the courage, even had they the ability, to attempt such an enormous task. Whatever the reason may be for this forbearance, the author cherishes

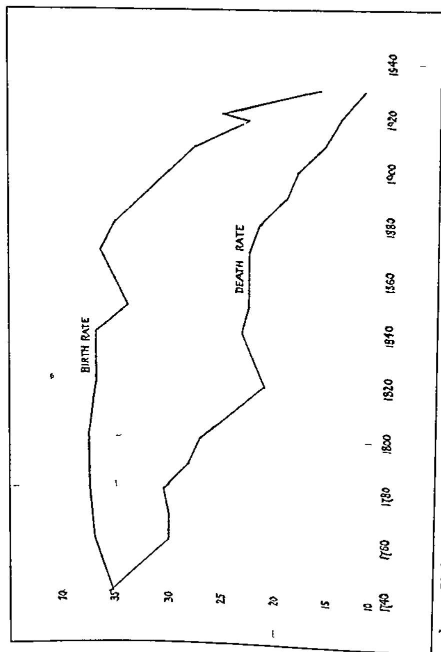


Fig 1 The birth rate and death rate per 1 000 of the population in England during the period 1740 1930 (after Carr Saunders in World Population)

the belief that the course of bacteriology that is given generally is suited to the needs of a man who is going to be a practitioner of medicine but it would be more aptly named the science of infectious disease

A clumsy and somewhat pretentious title it does describe more accurately the contents of such a course and although this review is written for the graduate and not for the student the underlying idea is the same Bacteriological details and technicalities are out of place in a general review and their omission also will make it easier to read

A survey of the mortality from infectious diseases in recent years shows a definite decline in countries with the health organisation characteristic of Western civilisation This decline is a continuation of a general trend which has had only one or two minor interruptions in the course of the last sixty years While the fall in mortality is due mainly to direct efforts to control infectious disease by improved sanitation by improved hygiene and standards of living and by mass immunisation we can not doubt that in some infectious diseases our efforts have been aided by a natural decline in the severity of the disease The most notable example of this is scarlet fever and there is evidence also that diphtheria showed a steady fall in mortality long before the introduction of antitoxin

A severe pandemic of influenza is the only serious epidemic disease of whose control we are still doubtful although of course it is always possible that a new and fatal epidemic disease like the sweating sickness of the 15th and 16th centuries may appear suddenly

What of the future? It is probable that the low point of the death rate is being approached if indeed it has not been reached already in some countries In Fig I is shown the general trend of the birth rate and the death rate in England in the last two centuries It will be seen that during the last fifty years the birth rate has fallen much faster than the death rate This means that the number of individuals in the upper age groups is increasing relatively to those in the lower age groups and since the death rate of the upper age groups is higher than that of the lower age groups an increase in the general death rate necessarily follows Against such an increase must be balanced any decrease due to a further improvement in the health of the community although any great improvement seems unlikely If the present trends of the birth rate and the death rate continue we must expect the birth rate to fall further and the death rate to commence to rise It seems inevitable that in the most highly developed countries the population will become stationary in the next ten or twenty years and then begin to decrease at first slowly and then more rapidly although by that time prophecy is verging into speculation as the fall in the birth rate may be halted It is ironical that the actual gain in population due to the control of infectious disease in the last fifty years perhaps the most brilliant era in the history of medicine bids fair to be more than balanced by the wholly unforeseen phenomenon

of a rapidly falling birth rate This is not the place to discuss the implications of a diminishing population nor the factors which lie behind the falling birth rate but the dangers are not yet realised generally in a world which is preoccupied with lesser but seemingly more urgent problems

Turning from the general to the particular a brief review is given of the recent developments in the scientific management of infectious disease

Methods of Diagnosis

In the diseases of bacterial origin the developments have been mainly in the direction of refinement of existing methods notably the typing of pneumococci streptococci diphtheria and typhoid bacilli The main benefit has been to improve our knowledge of the epidemiology and transmission of these infections Blood culture is carried out more frequently as it is realised that in many diseases this is also the most important prognostic test that is available the patient rarely being in danger diphtheria and tetanus excepted so long as the blood culture remains negative

The practitioner still is unable to diagnose accurately a large proportion of the infections which he sees in the course of his work The bacteriologist rarely is called upon for help but it must be admitted that in many of the less serious infections laboratory investigations are unable to throw any light on the diagnosis It is in the group of upper respiratory infections described rather than diagnosed as feverish colds or influenza that the clinician and the bacteriologist fail most often These* are perhaps the most common pyrexial infections of all in temperate climates and are continually passing from individual to individual The clinical symptoms are not sufficiently well-defined to permit of classification and it is unlikely that they will be classified properly until the etiology of these infections has been worked out It is generally believed that viruses are responsible and a beginning has been made with the isolation of the virus of influenza but much remains to be done

The problem of how to make the bacteriological laboratory more easily available to the practitioner is not yet solved but since it is a part of the much larger problem of the future organisation of medical practice it will not be discussed here

* The infectious cold is of course the most common of all upper respiratory infection but is not considered here as it is commonly apyrexial and the doctor usually is not called in unless there is a complication

Methods of Prophylaxis

The general purpose of sanitation is to prevent the access of pathogenic bacteria to human beings. The word sanitation rarely is used now in this general sense but has been restricted to methods of disposal of human excreta and refuse. It will not be used here in this restricted sense.

Alimentary sanitation, i.e. the protection of food and drink from dangerous contamination, has been well organised for many years and there are no new developments to report except the general spread of the practice of pasteurising milk, particularly in America. New legislation in England to encourage pasteurisation has been emasculated by vested interests. Further experiments have shown that pasteurisation does not lessen the value of milk as one of the most important of the protective foods.

Cleanliness is clearly a form of sanitation. Its greatest triumphs have been in surgery, for the aseptic technique is merely a meticulous cleanliness, and in typhus fever, which retreats as the bath room and the wash tub advance.

Aerial sanitation, i.e. the prevention of droplet infection, is a more difficult problem which has been largely neglected. Indeed it is only within the last few years that it has been even studied. W. F. Wells has shown that the main danger is from minute droplets less than 0.1 mm. in diameter, from which the water quickly evaporates, leaving a very light particle which remains suspended in the air for some considerable time. These droplets are expelled in great number whenever an individual speaks, coughs or sneezes. Masks will lessen the danger under special circumstances, such as in the operating room or during delivery and the early puerperium, but there is obviously a limit to the use of masks. In aerial sanitation there are two urgent problems to face: (1) how to control cross infections in infectious disease hospitals and to a lesser degree in children's hospitals[2]; (2) how to obtain a measure of control in schools, halls, cinemas, etc., where numbers of individuals are crowded together. In order to minimise the danger of droplet infection it is clearly desirable to reduce the number of infective particles in the air. This can be achieved either by sterilising the air or by diluting the infected air by ventilation, thus reducing the concentration of infective particles. In America attempts are being made to sterilise the air by ultra violet radiation either in the form of general radiation of the air in a room or in the form of a screen radiator between the beds in an infectious disease hospital. The results are said to be promising, but it is too early to say whether the radiation method will prove to be practical.

Favourable reports have been published recently on another method of sterilising the air in which a spray of a finely atomised antiseptic solution is used. The individual droplets are very small, about 1 to 2 microns in diameter, and remain suspended in the air for a considerable time. The antiseptic mist is called an aerosol by Trillat, who introduced the method.

There remains ventilation, to the desirability of which everyone pays lip service, but how often does one enter a ward of an infectious disease hospital or the dormitory of a school to find the beds far too close together. As Hobson has pointed out recently, there are standards laid down,* but little attention is paid to them and overcrowding is the rule rather than the exception in most institutions. The motive of economy cuts right across the first principle of aerial sanitation, the avoidance of overcrowding. The proper ventilation of schools, halls and cinemas is a much more difficult problem, prompting the experiments on physical and chemical methods of sterilising the air.

However much aerial sanitation may be improved, it is highly unlikely that its efficiency ever will approach that of alimentary sanitation, so that it will need to be reinforced always by immunisation of the susceptible population if the danger from the disease warrants such a measure. Now mass immunisation under the voluntary system is not a measure to be undertaken lightly, requiring sustained effort and enthusiasm both in the actual immunisation and in the education of the community to submit to it. It may be possible — the French Army have already put it into practice — to combine a number of immunising agents and inject them together. Time will show whether such a method is as effective and safe as it is desirable.

Methods of Treatment

Up to the year 1935 the only specific methods of treating infectious disease other than syphilis that had proven value was the injection of antisera, either antitoxic or antibacterial. The principle was logical, being an effort to supply the body with antibodies in the early stages of an infectious disease. In practice the results often were disappointing in many instances because the antisera were injected too late to influence the course of the disease. Another principle, that of destroying the parasite with a chemical substance, received a tremendous impetus from

* The English Board of Education recommends the following minimum space in dormitories, 700 cubic feet per person, 65 square feet per bed with 3 feet between the edges of adjacent bed.

the discovery of the arsenical treatment of syphilis by Ehrlich some thirty years ago. However, despite many attempts, efforts to extend the field of chemotherapy met with little success until recently. In 1935 Domagk introduced a dye under the name of *prontosil* with the claim that it was effective against streptococcal infections. The claim was confirmed, and it was not long before it was shown that prontosil after injection into the body was reduced to a simpler substance, para-amino-benzene-sulphonamide, shortened now to sulphonilamide, which was more soluble and was probably the active principle of prontosil, since it was just as effective. Moreover sulphonilamide had the great advantage over prontosil that it could be given by the mouth. A great number of other substances have been synthesised now and put on the market under various names, but the only one of these of proved outstanding value at present (March, 1940) is sulphapyridine, in which a pyridine ring is substituted. Sulphapyridine appears to be as effective as sulphonilamide in streptococcal infections and much more effective in pneumococcal infections. The administration of sulphapyridine has been shown to be the most successful treatment known in hæmolytic streptococcal, pneumococcal, meningococcal and gonococcal infections and in pyelitis due to the colon bacillus. It is claimed to be of some value in severe staphylococcal infections, and there have been some favourable reports on its effect in trachoma and lymphogranuloma inguinale, but more evidence is needed, since the viruses in general seem to be insusceptible to these drugs. The drug is not without its dangers, agranulocytosis being the most serious of the toxic manifestations. The concentration aimed at in the blood is in the neighbourhood of 5 mgm. per cent. (for further discussion of the sulfonamides see Chapt. XXX-A in Vol. IV.)

The mode of action of these drugs on bacteria is not yet fully understood. In the test tube, if the drug is added to a growing culture of susceptible bacteria, the organisms continue to multiply at the normal rate for some ten generations, and then multiplication ceases. The actual bactericidal action is weak, the main effect being the delayed bacteriostasis described above. One must assume that at the critical point the metabolism of the organism is interfered with, and growth ceases. In the body apparently the same phenomena occur, and in addition phagocytosis of the bacteria has been observed after some hours. If an infection is looked upon as an unstable equilibrium between the rate of multiplication of the parasite and the rate of destruction of the parasite by the cells of the host, then an agent which slows the rate of multiplication of the parasite will tip the balance in favour of the host. It appears to be more effective to slow down the multiplication of the organisms with

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The employment of vaccines for therapeutic purposes dies hard but is slowly fading out of the practice of medicine. Originally backed up by Almroth Wright's opsonic index, the therapeutic vaccine survived the proof that the opsonic index was unreliable. Essentially illogical, it probably owes its survival to (1) the fact that recovery from infection by natural means is the rule and not the exception and (2) the tendency of the profession to ascribe that recovery to the treatment the patient has received despite all warnings about the pitfalls in "propter hoc" reasoning. Therapeutic vaccines were introduced more than thirty years ago, yet no controlled animal experiments proving their value have ever been published. It is a clear cut issue, faith vs science.

Despite the vast amount of research that has been carried out on the infectious diseases, there still remain certain aspects of infection which are ill understood and largely ignored, although they have a distinct bearing on our understanding of these diseases.

The Toxic Products of Bacteria

With the exception of those organisms which secrete powerful exotoxins, we cannot pretend that we understand why patients often die as a result of infection. Lobar pneumonia is an example. The filtrate of a culture of pneumococci has no effect on a susceptible animal. It is stated sometimes that the endotoxin is responsible, but the autolysate of a pneumococcus culture is only weakly toxic. In the case of the typhoid bacillus the mucolipoid fraction of the organism is toxic for mice and may be responsible for the toxemia so characteristic of typhoid fever, although there is no proof of this. Possibly significant is the observation that invasive bacteria generally invade the blood stream before death, but it is not known whether this phenomenon is connected causally with the ultimate death of the subject or whether the die already is cast before it occurs.

The Incubation Period

What is going on in the body during the incubation period of an infectious disease? The incubation period is in general longer in the virus diseases than in the bacterial diseases, and a reference will be found to the incubation period in virus disease in Dr. Burnet's chapter (Chapt. II–A, Vol. I). In the shorter incubation periods, such as are characteristic of scarlet fever and diphtheria, it is understandable that the organism requires two or three days to overcome the local resistance, but the long

these drugs than to speed up their destruction by injecting antibacterial sera If the administration of the drug is suspended before the balance is set permanently in favour of the host the organisms begin to multiply again and a relapse occurs

Without question the discovery of these drugs has been the most important advance yet made in the treatment of infectious disease but the demonstration of their therapeutic power has been somewhat demoralising since in numberless instances the drugs have been administered without rhyme or reason It is not pleasant to contemplate the practice of medicine sinking even temporarily to the level of a thermometer and a bottle of tablets but that is the danger in the enthusiasm and confidence in a new and potent therapeutic agent the belief that it will cure anything and everything and that diagnosis is unnecessary It is clear already that these drugs have their limitations and are not without danger if given in the doses which are therapeutically effective Fortunately they are the subject of much intensive work and they loom large in the literature so that it should not be very long before they take their right and sober place in the therapeutic armamentarium

Had not sulphonilamide and sulphapyridine occupied the attention of the medical world more interest would have been aroused by the recent discovery by Dubos of a product of a certain soil organism capable of destroying all Gram positive pathogenic bacteria It is certainly a discovery of outstanding importance Dubos impressed by the capacity of bacteria to develop new ferments to meet their metabolic needs sowed pathogenic bacteria in specimens of soil over a period of two years At the end of this time he isolated a bacillus from the soil which was capable of killing Gram positive pathogens but it is uncertain whether the soil bacillus had this property originally or developed it in contact with the pathogens The latter possibility seems unlikely especially as the bactericidal activity is not due to a ferment Dubos found that a culture of the soil bacillus soon undergoes autolysis and from the autolysate can be isolated an active substance which is heat stable soluble in acetone but only very slightly soluble in water Its chemical nature as yet has not been completely determined but it is not a protein It is strongly bactericidal to all Gram positive organisms like the staphylococci streptococci pneumococci but has no action whatever on Gram negative bacteria It is non toxic in doses which will protect mice against injections of living pneumococci and it appears to be more effective than sulphapyridine in this respect No doubt it will be some time before it is available for experimental trial in human beings one of the chief difficulties being the insolubility of the substance in water

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incubation period of typhoid fever was difficult to explain until the investigations of Orskov indicated that the organisms do not pass straight down the alimentary tract and establish themselves in the Peyer's patches of the small intestine, as was supposed formerly, but take a devious course. They pass from the intestinal mucous membrane through lymphatic channels to the nearest glands. Thence via the blood stream they enter the endothelial cells of the liver and spleen. Multiplying in these cells they reinvade the blood stream and thus reach the Peyer's patches.

The Non-specific Factors in Immunity

Until we examine immunity more closely we are inclined to think of resistance to infectious disease as an absolute rather than a relative phenomenon, more marked in the adult than in the child, and that it is always the result of a previous attack of the disease. These views no doubt stem from the observation that the average child suffered from a long sequence of infectious diseases to which the adult is resistant, but actually the child 2 years to 15 years is relatively much more resistant than an adult to a first attack of an infectious disease.

The graph of the mortality from small-pox at different ages in an unvaccinated community shows that the mortality is lowest in the children. Similarly in pneumonia some recently published figures covering a ten-year period show the following case mortality percentages at different ages: 0–5 years 26 per cent, 6–10 years 5 per cent, 11–15 years 4 per cent, 16–25 years 11 per cent, 26–35 years 20 per cent, 36–45 years 30 per cent, 45 + years 45 per cent. It is the same picture in tuberculosis, and in typhus fever and yellow fever the contrast is still more marked, for these are deadly diseases in the adult but are likely to pass unnoticed in the child, at the same time conferring a specific immunity. This biological phenomenon of non-specific childhood resistance is clearly the natural method of acquiring specific immunity to the various pathogens with a considerable margin of safety and it obviously has a survival value. The explanation is unknown. A reasonable hypothesis would be that the cellular reaction to the infecting parasite is faster and more efficient in the child than in the adult, for this is borne out by the rapidity with which a simple injury, such as a cut, heals in a child. A known exception to the rule is diphtheria, which is rare in the adult, and generally this is ascribed to specific immunity. This explanation is based on one set of observations which is transcribed from one textbook to another. Actually several authors have shown that the majority of

young adults are Schick positive and the reason for their comparative immunity is unknown

The part that heredity plays in immunity always must be difficult to unravel By careful inbreeding Webster was able to raise one race of resistant mice and another race of non resistant mice This is course was accomplished by selective mating and is mentioned only to show that there undoubtedly is a heritable factor in immunity It is customary to ascribe the lack of resistance to tuberculosis in an isolated community to a lack of inherited resistance but one must remember that on first contact with tubercle bacilli there must be a large number of adults in such a community who have not been immunised by a childhood infection However many believe that certain families show a lessened resistance to tuberculosis and that this is evident even when the individuals are removed from a tuberculous environment

The nutritional factor in immunity seems so obvious — the steep rise in the tuberculosis mortality in Central Europe during the last war is a recent example — that it is rather surprising that there are no convincing animal experiments showing a decreased resistance when animals are deprived of the various vitamins with the possible exception of vitamin A In animal experiments however the animals usually are infected artificially but under more natural conditions in mouse colonies Webster has demonstrated that the diet does influence the mortality from a natural infection but however he did not analyse the various factors in the diet

The developments in each of the more common infectious diseases of bacterial origin will now be reviewed

Staphylococcal Infections

The proof that *Staphylococcus hæmolyticus* the pathogenic species of the organism secretes a soluble exotoxin naturally stimulated workers to explore the possibilities of antitoxic immunity although it is yet uncertain whether immunity to the staphylococcus is antitoxic or antibacterial or a combination of the two The injection of toxoid undoubtedly stimulates the formation of antitoxin and many believe that toxoid is valuable in the treatment of chronic furunculosis The enthusiasm about toxoid should be tempered by the knowledge that toxoid is the last in a long series of remedies that have been advocated for furunculosis Toxoid has been tried without success in the treatment of osteomyelitis in which disease incidentally the antitoxin content of the patient s serum often is raised far above the normal level Antitoxic serum has been tried in the treat

ment of staphylococcal bacteræmia but the evidence in its favour is not very convincing

While it is true that no striking advances have been made in our knowledge of staphylococcal immunity it is also true that these infections are apt to be chronic and to recur from time to time and it is therefore unlikely that artificial methods of establishing immunity will be found for our greatest successes with artificial immunity have always been achieved in those diseases like diphtheria and small pox in which the course is acute and in which if the patient recovers immunity is established firmly

When specific immunity fails us we naturally turn to chemotherapy The Germans have advocated the use of uleron one of the sulphonilamide drugs for staphylococcal infections but it has not become popular in England or America where it is claimed that sulphapyridine reduces the mortality in severe staphylococcal infections (see also Chapt XXX–A Vol IV) If the infection has progressed as far as pyæmia with multiple abscesses in the various organs it is doubtful whether any of these drugs can save the patient

Streptococcal Infections

In recent years there has been steady progress in our knowledge of these infections and latterly a brilliant advance in their treatment

The classification of the chain forming cocci although not yet complete at last rests on a firm basis thanks to the work of Brown Lancefield and Griffith Brown worked out the primary classification into hæmolytic and non hæmolytic streptococci and it is only rarely that the latter are pathogenic in man

Rosenow and his followers still maintain that non hæmolytic streptococci are the etiological agents in a variety of human ills but their claims have not been confirmed by other workers The only disease in which we are certain that they are the etiological agent is infective endocarditis where they infect malformed or damaged heart valves apparently because the local cellular reaction to the parasite is impaired under these conditions Non hæmolytic streptococci commonly are isolated from the apices of extracted non living teeth and while many believe that such a finding is significant others are more sceptical In the first place control extraction of healthy living teeth indicates that it is doubtful whether the isolated organisms come from the apex of the dead tooth or from the saliva and mucous membrane in which they are present in enormous numbers In the second place even if such streptococci were connected

causally with apical granulomata there is no good evidence that these lesions are any more than a local reaction to a feebly pathogenic parasite It is probable that the role of these apical lesions in causing various chronic ailments has been exaggerated because the lesions are detected so easily and correction is so simple At best the removal of such foci of infection is a gamble and it should not be forgotten that serious interference with mastication may bring other evils in its train

There is on the other hand no doubt whatever that some hæmolytic streptococci are pathogenic Apart from the actual lesions the habitat of the hæmolytic strains is the nasopharynx and they are isolated frequently from the throats of healthy carriers The question then arises Is a carrier of any hæmolytic streptococcus a potential danger? Lancefield s antigenic classification of the hæmolytic streptococci has enabled us to answer this question with some assurance She has shown that hæmolytic streptococci can be divided into various groups (A B C etc) and of these groups Group A contains the humanly pathogenic strains while Group B Group C and Group G strains although occurring frequently in the human nasopharynx rarely give rise to disease in man Hence a carrier of a Group A strain is a potential danger but a carrier of a Group B Group C or Group G strain can be ignored Lancefield s classification depends on a specific group carbohydrate obtained by making an acid extract of the organism which forms a precipitate when added to the corresponding group antiserum Griffith has carried the classification of Group A hæmolytic streptococci a stage further by establishing some twenty five different types distinguishable by a slide agglutination test The work of Lancefield and of Griffith has been invaluable in the epidemiology of streptococcal infections since it is possible now to identify most strains of hæmolytic streptococci and thus to trace the source of an infection or to map an epidemic

The most common of the diseases caused by *Streptococcus hæmolyticus* is acute tonsillitis or pharyngitis with or without a rash The belated discovery of the ætiology of scarlet fever gradually is placing this exanthem in its true perspective Whether or not a patient suffering from a streptococcal sore throat shows a rash depends on two factors (1) the amount of erythrogenic toxin produced by the infecting strain of hæmolytic streptococcus (2) the amount of the corresponding antitoxin in the patient As regards the first factor the majority of the types of hæmolytic streptococci can cause scarlet fever although some types are associated more commonly with the disease probably because they secrete more of the erythrogenic toxin In connection with the second factor antitoxic immunity protects only against the rash not against an acute

streptococcal tonsillitis or pharyngitis Recognition of these facts is essential in any attempt to control streptococcal infections by isolation From five to ten per cent of the community are carriers of Group A hæmolytic streptococci but while these individuals are a potential danger certainly they are not as dangerous as the individual with an acute infection These patients with an acute infection should be isolated irrespective of whether they have a rash but it is still a common practice to remove the patient with a rash to an infectious diseases hospital while the patient with a streptococcal sore throat remains at home usually with no attempt at isolation As Hobson has pointed out this practice is quite illogical as both patients are equally infectious Even in hospitals a surgeon would be horrified if a patient who developed scarlet fever was not removed from a surgical ward to isolation but he commonly ignores the danger from a patient with say a discharging ear despite the fact that several ward epidemics have been traced to such a source

At the present time scarlet fever is a mild disease yet a hundred years ago it was the most feared of all the infectious diseases One might be inclined to think that the present mildness was a permanent change were it not that fluctuations in severity have been characteristic of the disease throughout its history Why had scarlet fever so high a case mortality in the nineteenth century? There are two possibilities (1) that the organisms were more toxic (2) that the organisms were more invasive While the first possibility cannot be discounted the toxin as we know it is very weak compared to the toxins of the diphtheria and tetanus bacilli and we know also that a streptococcal infection only becomes dangerous when there is a general invasion via the blood stream Admittedly it is a guess but in the opinion of the author the second possibility is the more probable

It is customary to give the specific antitoxin to scarlet fever patients if the symptoms are judged to be severe and most authors speak favourably of it Antitoxin has the reputation in some quarters of preventing the onset of that dangerous sequela acute nephritis but the incidence of nephritis in untreated scarlet fever patients is so small about one per cent that a very large number of cases would be necessary to yield significant figures in a properly controlled experimental trial Although it would be possible to immunise the community actively against the rash of the scarlet fever syndrome one obviously would not be justified in advocating it under the present conditions

We remain in doubt as to the pathogenesis of two sequelæ of acute streptococcal tonsillitis or pharyngitis viz acute glomerular nephritis and acute rheumatism The course of events is similar in both the

temperature subsides there is a silent period of two to three weeks while the patient apparently is convalescing normally and then the nephritis or rheumatism supervenes Indeed all recent work suggests that both acute glomerular nephritis and acute rheumatism are preceded always by a hæmolytic streptococcal infection but the actual connection between the infection and the sequelæ is obscure Since acute nephritis rarely is associated with acute rheumatism it would appear unlikely that there is a common basis in the pathogenesis of the two conditions despite the similarity in the prodromal events The most favoured theory is that these sequelæ are a manifestation of allergy If by allergy is meant that form of hypersensitivity anaphylaxis which is associated with an interaction between an antigen and its specific antibody there is a certain amount of indirect evidence

In the case of acute rheumatism we might suppose that antibodies are being formed in the silent period just as in serum sickness the symptoms of which bear some resemblance to the symptoms of acute rheumatism We know that serum sickness is due to an antigen antibody reaction in the tissues and by analogy we might infer that acute rheumatism has a similar basis although at best this is only a working hypothesis Coburn and Pauli have shown lately that the serum in different stages of acute rheumatism contains an antigen and an antibody but their identity has not been established nor is it clear how an anaphylactic reaction could lead to organic changes in the heart or maintain a prolonged pyrexia Acute rheumatism has more the ear marks of an active infection and in this connection mention should be made of some observations that have been made lately by two independent workers Green and Collis made cultures from the heart valves of a number of subjects with acute rheumatism that came to autopsy From the majority hæmolytic streptococci were grown although blood cultures from the same subject were sterile The significance of this finding has yet to be determined It may be that under special circumstances normal heart valves can be infected by hæmolytic streptococci and the result is the nodular lesion characteristic of acute rheumatism These lesions are firm and the blood stream remains sterile If however the valves are either malformed or damaged by previous infection a number of different organisms can infect them giving rise to vegetative infective endocarditis Here the lesion is much more friable and the organisms are found in the blood stream Against the simple theory that acute rheumatism is a delayed infection of certain structures in the body with hæmolytic streptococci is the fact that sulphonilamide has no effect on the course of the disease

Several workers have been investigating another hypothesis that

rheumatic fever is caused by a virus Very small particulate bodies found in pericardial exudates of patients dying of rheumatic fever appear to be agglutinated by the serum of patients suffering from the disease While such observations are interesting the authors recognise that they are not conclusive In all of these attempts to elucidate the etiology of rheumatic fever the outstanding difficulty is the impossibility of reproducing the disease in animals for always there must be an element of doubt about indirect evidence

In the case of acute glomerular nephritis there is indirect evidence that an antigen antibody reaction is going on somewhere in the body for several observers have shown that the complement in the serum is diminished and it would be reasonable to suppose that the complement in the body has undergone antigen antibody fixation The œdema which may precede the kidney signs might be explained as a histamine effect (the liberation of histamine is known to result from an anaphylactic reaction) although the author can find no record in the literature of any investigation on this point in acute nephritis

The teaching of Lister foreshadowed by Semmelweiss and Holmes lowered the incidence of puerperal sepsis but did not eliminate the disease The problem was not investigated thoroughly until the last decade when Meleney and Smith pointed out that many infections could be traced to droplet infection from the nasopharynx of the attending doctor nurse or even of the patient herself Meleney s attention was directed to this source of infection by the simultaneous occurrence of an outbreak of streptococcal sore throat among the staff and of puerperal sepsis among the patients in a lying in hospital The aseptic precautions that have been the ordinary routine in the operating room for many years were not then carried out in the delivery room or in the labor wards Masks were not used at all and perhaps only the doctor was gloved We realise now that asepsis should be even more rigid during delivery and the puerperium than in the operating room because the uterus under these conditions is particularly prone to infection with the hæmolytic streptococcus An additional precaution since masks are not infallible is the prohibition of any contact between carriers of Group A hæmolytic streptococci and these patients Since often it is impracticable to carry out frequent routine examination of all the staff of a hospital for the presence of Group A hæmolytic streptococci perhaps the best compromise is to insist that the staff report immediately a cold a sore throat a discharging nose or ear or any infected cut or sore Group A hæmolytic streptococci are never found in the vagina before delivery an additional proof that infection always is exogenous Anaerobic non hæmolytic streptococci

on the other hand are found normally in the vagina and can infect the uterus if there has been trauma during delivery the dead tissue forming a suitable nidus for the multiplication of the organism Diagnosis is made by anaerobic blood culture The sulphonilamide drugs unfortunately do not influence the anaerobic streptococcal infections

Sulphonilamide and sulphapyridine have revolutionised the treatment of severe hæmolytic streptococcal infections but it is doubtful whether these drugs are necessary in mild infections So far in controlled series of cases there is no convincing evidence that *sulphonilamide influences the course of scarlet fever If further work confirms this observation the* reason may be that the lesion of scarlet fever at the present time is a superficial one and there is no tendency on the part of the organism to invade If scarlet fever again increases in severity and it is shown that the organisms are more invasive we would expect sulphonilamide to be of the greatest value In erysipelas cellulitis meningitis and puerperal sepsis sulphonilamide is indicated definitely particularly when the blood culture is positive Before the sulphonilamide era patients with this evidence of generalisation of the infection had no better than an even chance of recovery whereas now a days one is surprised if the patient does not recover Sulphonilamide resistant strains of hæmolytic streptococci have been reported but an unsuspected infective endocarditis is often the explanation of the failure of the drug Streptococcal meningitis furnishes the best proof of the value of sulphonilamide Formerly it was almost always fatal while now a days although it still is a dangerous disease there is a good chance of recovery

An interesting disease to investigate in this connection is small pox *The secondary fever of small pox is due to the infection of vesicles with bacteria usually hæmolytic streptococci and if the resulting pustules are* confluent the prognosis is grave A few cases have been reported in which under treatment with sulphonilamide the vesicles have dried up without becoming infected and no secondary fever has occurred In the most malignant forms of small pox the patient dies in the primary fever stage presumably from the virus itself but death in the great majority of instances is due to the secondary infection Sulphonilamide could never be a *rival to vaccination in the control of small pox but it might be a very valuable adjunct if the secondary infection could be prevented*

Similarly in the peculiar form of bronchopneumonia often called heliotrope pneumonia which follows influenza there is some evidence that the hæmolytic streptococcus is implicated If this should be confirmed in the next epidemic of severe influenza we might hope here too for a therapeutic advance

Perhaps one of the greatest disappointments with sulphonilamide has been its failure in the treatment of acute rheumatism

Pneumonia

During the last twenty years pneumonia and the pneumococcus have been the main interest of a very large number of investigations particularly in America Progress has been steady in the antigenic analysis of the organism the development of specific serum treatment the routine typing of the infecting strains and finally the preparation of type specific rabbit antisera against all the known types some thirty in number The case mortality diminished with serum treatment but under the normal conditions of practice it seemed that the mortality in treated cases could not be reduced to much less than sixty per cent of the mortality in untreated cases It is true that if the patient received the serum in the first twenty four hours of the illness the mortality was considerably lower but even if the diagnosis could be made promptly and the sputum could be typed immediately one could not count on the physician being called in at once especially as many pneumonias have a slow onset indistinguishable from an ordinary upper respiratory infection Time thus was the most important limiting factor in the serum treatment of pneumonia and in places distant from centres of population there were always the difficulties of typing and of the supply of type specific serum

Upon this scene in 1938 came the announcement of the effect of a new drug sulphapyridine on experimentally infected mice and on pneumonia patients Even allowing for the enthusiasm with which every new drug is hailed there is no doubt that sulphapyridine is an advance on serum treatment and since the drug can be given by mouth acts against all types of the pneumococcus and appears to be effective later in the disease than a serum it became the treatment of choice within a year of its introduction Present indications are that the general i e all age groups combined case mortality in patients adequately treated with sulphapyridine will fall below ten per cent It is yet too soon to say whether even better results will be possible with a combination of serum and drug treatment but some animal experiments point in this direction The action of the drug appears to be purely bacterio static and antibodies do not appear according to Wood and Long until some days after the temperature has fallen This would explain why a relapse is apt to occur if the drug is discontinued too soon

Circumstantial evidence points to the importance of chilling in precipitating an attack of pneumonia but it is not known how chilling lowers

resistance. A recent experiment with immune animals kept under the influence of alcohol showed that they could be infected under these conditions and that the local cellular reaction was lacking. It is possible that chilling may act in the same way.

Gram-negative Cocci

The Meningococcus — Meningococcal meningitis is a disease which is normally endemic in very young children but small epidemics occur from time to time in adults especially under conditions of overcrowding. These epidemics have been shown to be associated with a very high carrier rate in the community, twenty per cent or over. This is another of the diseases in which a fairly successful anti-serum treatment has given way to still more successful and a much easier treatment with sulphonilamide and sulphapyridine. Intrathecal administration of the drug is not necessary since it is found in considerable concentration in the cerebrospinal fluid soon after oral administration.

It may be remarked in passing that no really effective method has been found for the treatment of meningitis caused by the influenza bacillus, a not uncommon infection in very young children. Occasionally a patient recovers after treatment with antiserum or with sulphapyridine or with both, but the majority of these patients die. The meningitis appears to be more widespread than in meningococcal meningitis and there is a greater tendency to pocketing.

The Gonococcus — Until the introduction of sulphonilamide little had been achieved in the control or treatment of gonorrhœa since the discovery of the organism. Although one of the most important and widespread of all human diseases, gonorrhœa always has been the Cinderella of the infectious diseases in the eyes of the medical profession. If we have an effective method of treatment it is to be hoped that the problem of eliminating gonorrhœa or at any rate of greatly reducing its incidence will be taken up seriously without prejudice and without moral red herrings. Moreover there is an encouraging precedent: with the exception of a temporary rise after the demobilisation of the troops in the last war, the incidence of syphilis has declined steadily since the introduction of arsenical treatment. Still better results should be achieved in gonorrhœa, which in most cases is claimed to be cured easily and expeditiously by one or other of the sulphonilamide drugs. Several of these drugs are under trial in order to find out which of them is the most satisfactory under the special conditions. These patients are rarely confined to bed — it might be better if they were, but this is generally impracticable — and

are only seen at intervals so the relative toxicity of the drug is important Another difficulty is one that is always associated with out patients the patient thinks he is cured after a few days and ceases attendance at the clinic and all experience with these drugs points to the danger of stopping treatment too soon The possibility of toxic accidents and of relapses due to incomplete treatment are difficulties which are unavoidable but they can be minimised by an efficient organisation of the clinic Perhaps more could be done in relieving and preventing ill health in this field of medicine than in any other but enthusiasm good organisation and strict laboratory control are essential in the clinic if results are to be achieved Cinderella still awaits the good fairy

Diphtheria

Despite the universal use of antitoxin diphtheria continues to take its toll of lives The deaths may occur in the first few days of the disease or more commonly about the end of the second week While there is no doubt that the toxin is responsible for all the symptoms of the disease the pharmacology has never been worked out accurately Now that methods of purifying the toxin are available (Eaton and Pappenheimer) doubtless this will be done The purified toxin is extremely powerful Pappenheimer stating that 1/10 000 000 mgm is sufficient to elicit a skin reaction It is generally believed that death is due to myocardial poisoning although signs of peripheral circulatory failure during life and signs of adrenal lesions after death in both animals and man have roused suspicions that disturbances of the adrenal secretions may play an important part in the syndrome of fatal diphtheria

McLeod and his colleagues showed several years ago that severe diphtheria almost always was associated with two bacteriological types of the diphtheria bacillus the gravis and intermedius types while the mitis type rarely caused more than a mild form of diphtheria All three of these types form the same toxin but apparently the gravis and intermedius types on occasion form more toxin or form it at a faster rate Fortunately not all gravis and intermedius infections are severe but the very severe forms of the diseases often called malignant diphtheria, carry a high case mortality in spite of large doses of antitoxin In malignant diphtheria the throat lesion is extensive the draining lymph nodes are swollen there is a fœtid odour a nasal discharge and the patient shows profound prostration Examination of the blood serum in a few cases of severe diphtheria before the administration of antitoxin has shown the presence of free toxin in the circulation while in the ordinary case of

mild diphtheria free toxin is absent The failure of antitoxin in malignant diphtheria can be explained thus the patient has received a fatal dose of toxin before the antitoxin is administered The necessity of giving antitoxin at once and by the intravenous route in severe diphtheria is emphasised once again Speed probably is of far greater importance than the amount of antitoxin Madsen in Denmark withheld antitoxin in 25 cases of mild and moderate diphtheria and studied them carefully Recovery took place in all without incident and the amount of antitoxin that was formed naturally was quite small This study and the observation that in mild diphtheria the blood contains no detectable toxin suggest that antitoxin is unnecessary in the milder forms of the disease but since it does no harm obviously it is safer to give it in every instance Time is the limiting factor in the antibody treatment of diphtheria as in all infectious disease and it has long been recognized that we can reduce but we cannot eliminate the danger from diphtheria by the use of antitoxin

A large percentage of children are immunised naturally by slight infections which never reach symptom level This natural method can be made safe by artificially immunising the susceptible children in a community with toxoid Three injections of toxoid or two injections of toxoid precipitated with alum confer an immunity against diphtheria which is quite satisfactory although not absolute It is desirable that the injections be well spaced at least one month apart and if the child is immunised when it is one or two years old another injection should be given on entering school A great deal of evidence is accumulating that if prophylactic immunisation is carried out thoroughly in a community diphtheria can be eliminated What percentage of children in a community have to be immunised before one can expect a real diminution in the incidence of diphtheria? In other words what is the effective inoculation rate? This is a question which should be faced more often than it is at present Ledingham in a recent paper has put this rate as high as eighty per cent Unless inoculation is made compulsory it is not easy to reach this figure in practice but it can be done if the public health authority makes a sustained effort to overcome the apathy and ignorance of the parents The author ventures to disagree with Ledingham who advocates compulsion and feels that the voluntary system should be retained The arguments for compulsion are strong particularly the argument that it is the child who suffers and not the careless parent but the voluntary cooperation of the parents can be obtained if a sustained effort is made and the democracies have an innate suspicion of compulsion which is not unjustified Very few individuals very few

authorities are able to use power wisely and sooner or later it is abused

Pertussis

Again and again it has been pointed out that whooping cough ranks next to diphtheria and in some years above it, as the most dangerous disease of early childhood Yet always there has been a curious apathy about this disease and only here and there has any attempt been made to investigate the problem of controlling it A second attack of whooping cough is not common so that a priori it should be possible to protect children artificially

Vaccines of various kinds have been used in prophylaxis the most important advance being made by Leslie and Gardner who showed that recently isolated cultures of pertussis organisms were all identical but after cultivation on artificial media for some time they underwent an antigenic change As a result of this work vaccines always are prepared now a days from recently isolated organisms Sauer in America has stressed the importance of larger doses and advocates the injection of a total of 80 000 million organisms Three or four injections are given and there is little reaction

How is immunity to be assessed? One can gain indirect information by animal experimentation or one can vaccinate a number of children and then observe whether these children show a greater degree of immunity than a corresponding number of unvaccinated children when exposed to infection Immunity experiments in animals have not been very helpful in the past Animals have a relatively high resistance and the minimum lethal dose of organisms is so high that immunity is difficult to demonstrate Lately Burnet and Timmins introduced a new technique of infecting mice by nasal insufflation the animals being examined some days later for evidence of consolidation and the presence of organisms in the lungs This method has been developed further by Keogh and North and promises to be a much more delicate method of registering degrees of immunity and of investigating important problems the nature the mechanism and the duration of pertussis immunity

A few groups of workers in America have been carrying out field observations on the value of prophylactic vaccination This has been done very carefully and thoroughly and has entailed a great deal of patient work over a number of years Their conclusions have been restrained but they have amassed already a body of evidence which suggests that while prophylactic vaccination does not confer absolute

protection which is not to be expected the attack rate has been reduced to about twenty five per cent of that of the unvaccinated children and that when a vaccinated child does contract whooping cough the attack is likely to be mild in nature The duration of the immunity is uncertain but if the child is vaccinated originally at the age of six months a single reinforcing injection is suggested at intervals of eighteen months or two years This work has resulted in a valuable addition to our knowledge and it is to be hoped that in time the profession in general will be roused to take active prophylactic measures against this disease In cases of emergency the injection of adult or convalescent serum has been advocated as a temporary prophylaxis but until such time as the protective titre of the serum is evaluated this procedure necessarily must be haphazard

It has been known for a long time that whooping cough can be diagnosed bacteriologically some seven to ten days before the first whoop and that it is during this period that the disease is most infectious but the diagnostic service that has been running in Denmark for many years has never spread to other countries except in isolated places This is due no doubt partly to the apathy about prevention partly to the absence of any specific remedy for the disease Claims have been made from time to time that vaccine administered during the disease mitigates the cough but controlled trials have not upheld these claims

THE ENTERIC INFECTIONS

The new developments here have been on the theoretical side since the practical control of these infections is only a matter of enforcing well known sanitary precautions concerning the food and water supplies or if that is impracticable of immunising the population at risk of contracting these infections

However the basis of immunity against typhoid fever still is controversial Felix has demonstrated a labile antigen on the surface of virulent typhoid bacilli which he has called Vi antigen Felix believes that immunity is dependent mainly on the antibody against this labile surface antigen Other workers have extracted a stable mucolipoid antigen from the body of the bacillus and believe that immunity is dependent on the corresponding antibody The presence of the Vi antigen appears to be correlated with the resistance of the organism to phagocytosis while the mucolipoid antigen definitely is toxic so it is possible that both antibodies are concerned in immunity to the typhoid bacillus the Vi antibody being antibacterial the mucolipoid antibody being antiendotoxic

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the course of the disease but the evidence although promising is far too scanty to draw any sound conclusions as to the value of the drug

The Anaerobic Infections

Tetanus — Active immunisation against tetanus by injection of tetanus toxoid has been developed by the French and is now a routine practice in the French army The British Army recently has followed suit Unfortunately there is no simple test like the Schick test in diphtheria to determine whether an individual is immune The amount of tetanus antitoxin in the blood can be determined but this titration could only be carried out on a limited number of individuals Since the amount of antitoxin which is present several months after immunisation may not be sufficient for protection an additional injection of toxoid is recommended as soon as possible after the soldier is wounded The present war will determine whether this procedure is any improvement on the well tried prophylactic injection of tetanus antitoxin Theoretically the injection of toxoid has the advantage that sensitisation to horse serum is avoided but in the last war many thousands of soldiers had two and three injections of antitoxin without untoward results An anaphylactic reaction on the injection of serum is so dramatic that its frequency tends to be exaggerated In civil life the incidence of tetanus is not high enough to warrant the general introduction of active immunisation

Cole and Spooner in the Quarterly Journal of Medicine 4 295 1935 have made a careful study of the treatment of tetanus and from their evidence argue that if one adequate dose of antitoxin is given subsequent injections are unnecessary and perhaps harmful

Gas Gangrene — In the war of 1914–1918 the three principal causes of deaths from wounds were (1) hæmorrhage and shock (2) gas gangrene (3) sepsis which is a vague term but probably the *Streptococcus hæmolyticus* was the most dangerous organism concerned In the present war it is hoped that the mortality will be reduced by immediate transfusion to combat hæmorrhage and shock and by the administration of one of the sulphonilamide drugs to combat sepsis What can be done to combat gas gangrene? Before wounds were subjected to débridement in the advanced clearing stations the incidence of gas gangrene was as high as twelve per cent After debridement was instituted as a routine practice the incidence fell to as low as one per cent Can this be improved upon? That is doubtful at present because we do not know the value of prophylactic injections of gas gangrene antitoxin The principal cause of gas gangrene the Welch bacillus forms a toxin but it differs from the

The practical importance of this argument lies in the choice of the immunising agent for prophylactic vaccination and in the possibility of developing a therapeutic antiserum Should one use a vaccine of virulent organisms that have been treated so gently in the process of killing that the labile Vi antigen is preserved or should one use the mucolipoid antigen? Common sense whispers that we should be very sure of the new mucolipoid extract before we give up the vaccine of whole organisms that has served us so well in the past

Craigie has made a distinct advance in the epidemiology of typhoid fever he has shown that typhoid bacilli indistinguishable in other respects can be differentiated by their susceptibility to various bacteriophages By this method of identification it is possible to trace epidemics to their probable source

The prevalence of infantile summer diarrhoea continues to show a gratifying fall in the last decade despite the fact that we are still uncertain as to the etiology of the disease and have taken no specific measures against it Various reasons have been given for the decline in this disease particularly the better safe-guarding of milk such as pasteurisation and the use of the refrigerator However it is likely that the disappearance of the horse from cities has been an important factor For that has led to a great diminution in the number of flies and flies are largely responsible for the contamination of the milk in the home the organisms multiplying rapidly in the milk if it is not kept cold

Brucellosis

The diagnosis of this disease presents considerable difficulties and this fact hinders a reliable estimate of its incidence The *Brucella abortus* commonly is found in raw milk and while those who drink the infected milk rarely contract the clinical disease subclinical infections appear to be common enough if one judges by the raised agglutination titre in the serum of consumers of raw milk The disease is seen more often in those individuals who are associated with cattle and pigs in their daily work The diagnosis can be established with certainty by blood culture but while it is comparatively easy to cultivate the porcine strains from the blood one is not often successful with the bovine strains There remains the agglutination titre of the patient s serum The titre in healthy individuals rarely rises to 1 80 so that this titre is suggestive in a patient with an unexplained pyrexia It is wiser however to repeat the test at intervals since the titre usually rises higher in the active disease Claims have been made that the sulphonilamide drugs shorten

the course of the disease but the evidence, although promising, is far too scanty to draw any sound conclusions as to the value of the drug.

The Anaërobic Infections

Tetanus.—Active immunisation against tetanus by injection of tetanus toxoid has been developed by the French and is now a routine practice in the French army. The British Army recently has followed suit. Unfortunately there is no simple test like the Schick test in diphtheria to determine whether an individual is immune. The amount of tetanus antitoxin in the blood can be determined, but this titration could only be carried out on a limited number of individuals. Since the amount of antitoxin which is present several months after immunisation may not be sufficient for protection, an additional injection of toxoid is recommended as soon as possible after the soldier is wounded. The present war will determine whether this procedure is any improvement on the well tried prophylactic injection of tetanus antitoxin. Theoretically the injection of toxoid has the advantage that sensitisation to horse serum is avoided, but in the last war many thousands of soldiers had two and three injections of antitoxin without untoward results. An anaphylactic reaction on the injection of serum is so dramatic that its frequency tends to be exaggerated. In civil life the incidence of tetanus is not high enough to warrant the general introduction of active immunisation.

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tetanus bacillus in that it is a capsulated organism which can and does invade the tissues. This doubt about the value of the antitoxin is responsible for the suggestion that sulphonilamide in full doses should be given prophylactically, for animal experiments hold out the hope that the drug may be effective. In civil life gas gangrene is much less common than on the battlefield. Prophylactic injections of antitoxin are given rarely and while large doses of antitoxin are given always in treatment it is difficult to assess the effect. Further war experience may throw some light on the perplexing problem of the respective values of antitoxin, sulphonilamide and surgery in both the prophylaxis and treatment of the disease.

Tuberculosis

Although the gradual decline in mortality from tuberculosis continues, the rate for females in the 15 to 25 age group does not share in the decline for some unexplained reason, and in some cases it actually shows a slight increase. Similarly the percentage of tuberculin positive individuals at various ages is dropping, so that the observation at the beginning of the century that almost all adults show evidence of infection is true no longer. Indeed it is a matter of some concern that many medical students and probationer nurses, who from the nature of their work are exposed to more than average risk of contracting the disease, are tuberculin negative, for several studies have shown that tuberculin negative individuals apparently have less resistance than tuberculin positive individuals. It would be more dangerous for nurses to be tuberculin negative because they fall into the most susceptible age group for females, 15 to 25 years, the most susceptible age group for men coming much later in life, 45 to 55 years.

The statement that allergy is correlated with increased resistance is not yet accepted universally, and in any case must not be taken to mean that allergy is necessarily the cause of the increased resistance, one school even maintaining that allergy may be harmful. Animal experiments are contradictory, but the balance of evidence indicates that there is no causal connection between allergy and increased resistance. It must be admitted that our knowledge of the processes of immunity in tuberculosis is almost negligible, antibodies apparently playing little or no part.

Whatever the mechanism of resistance may be, there is no question that it is safer to acquire a first infection during childhood, the most resistant period of life, and it is reasonable to believe that this is the

natural method of acquiring immunity against active tuberculosis in later life when man is more susceptible. However this immunity is not absolute and active tuberculosis does occur in tuberculin positive individuals with old latent lesions. What is the pathogenesis of this form of active tuberculosis? Is it a fresh infection from without or is it due to a lighting up of the old latent lesion? There is no general agreement on the answer to these questions. One would have thought that a careful study and follow up of a large number of married couples of whom one partner acquired active tuberculosis would have given a definite answer. However here again the results of such studies are contradictory. It is probable that active tuberculosis in an individual with a latent lesion can arise in both ways and it must be left to the future to determine which is the more common mode.

The only advance in the laboratory diagnosis of tuberculosis is in the examination of the gastric contents for tubercle bacilli when sputum cannot be obtained in the ordinary way. Guinea pig inoculation still is the method of choice when the organisms are few in number despite the claims that have been made for cultural methods especially from the urine. The cultivation of acid fast bacilli from the urine is only presumptive evidence of the presence of tubercle bacilli and proof of pathogenicity is necessary to establish the diagnosis.

The steady decline in the incidence of tuberculosis has raised the hope that tuberculosis can be eliminated ultimately and undoubtedly there is still room for improvement in our methods of control. Opie and his colleagues point out that tuberculosis is mainly a familial disease probably because active tuberculosis is only initiated by repeated contacts. Routine examination of familial contacts and others at special risk such as medical students and nurses is most desirable in order to pick up the early cases. The net could of course be stretched more widely if money was available. Indeed the control of tuberculosis to a great extent turns on how much money the health authorities are prepared to spend on it for the raising of the nutritional and housing standards of all classes in the community for organised attempts to detect early cases for provision of adequate sanitarium accommodation for all the patients likely to benefit by it for provision for the dependents of sanitarium patients for suitable employment for those in whom the active disease is arrested. This is an expensive programme and few communities will face more than part of it and all the time careful watch should be kept on the statistics of the disease for there is the possibility that such an ideal programme might do more harm than good in the long run unless it were combined with artificial immunisation. For in eliminating the

tubercle bacillus we are interfering with the natural method of immunisation and we know that tuberculosis can spread rapidly in a non tuberculised community It is even possible that we are approaching the danger point already and the stationary or rising incidence in the female 15 to 25 years age group may be a straw in the wind We could combat this no doubt by immunisation with a vaccine of dead virulent organisms or with Calmette s living attenuated vaccine although one does not contemplate another mass immunisation with any enthusiasm The subject is mentioned here because in pursuing our goals in public health we are apt to be somewhat naive and to think that we can interfere with biological phenomena with impunity

SYPHILIS

The number of fresh syphilitic infections also shows a decline in most countries although less marked in America where the incidence in the negro part of the population remains high There seems little doubt that regular and prolonged treatment now recognised as essential is responsible This progress towards ultimate control of the disease is a tribute to steady and patient therapeutic effort

The spate of diagnostic serum reactions has died down and the Wassermann complement fixation reaction and the Kahn and Kline flocculation reactions are now established in most centres The flocculation reactions are more sensitive in treated cases but occasionally break down because of an inhibition zone giving a false negative reaction With serums on the border line different laboratories will return different findings even if the same reagents and technique are used The nature of the reacting substance in the serum still is unknown its absence on one or two occasions is certainly not proof of cure and its amount does not always run parallel with the apparent activity of the syphilitic lesions Experienced observers believe that individuals with latent syphilis i e individuals with no evidence of active syphilis but with a positive serum reaction are potentially dangerous It is obvious also that the clinical finding of ' no active syphilis always must be open to question since the most painstaking clinical examination never can be very searching

It is curious that the prophylactic injection of neoarsphenamine has never been pushed as a means of controlling the disease If the drug is given within 24 hours perhaps even 48 hours of exposure it appears to be effective in preventing infection It has been said that this prophylactic injection might result in a masked infection but it is doubtful whether this is a serious danger and it is surely a risk that is worth

taking especially if the patient is warned to present himself for blood examination three months later

Actinomycosis

These infections particularly in the cervicofacial region are more common than is generally realised The usual history of a patient with cervicofacial actinomycosis is that a tooth was extracted and then after a varying interval a swelling was noticed in the neighbourhood of a tooth socket In most cases the abscess bursts externally healing occurs fairly quickly and the cause of the lesion is not revealed unless it is investigated bacteriologically at the time More rarely a sinus persists for some months and sooner or later the diagnosis is established It is curious that the upper jaw rarely is affected The organism is present in many mouths as a potential pathogen It is microaerophilic and presumably the connection between dental interference and infection is due to the fact that the organism can only flourish in devitalised tissue

Dental Caries

Dental caries might be considered as the sole concern of the dental profession but the family physician can hardly shelve the responsibility Everyone would agree that the almost universal dental decay characteristic of civilised races is a standing disgrace to both dental and medical professions Within the last decade much more intensive study of this problem has been carried on mostly in America and the standard of the work has improved proportionally No agreement has been reached yet as to the etiology of dental caries nor on methods of prophylaxis

Few would cavil at the statement that the tooth enamel is destroyed by acid which is formed as the result of fermentation of the carbohydrates in food by certain groups of organisms in the mouth notably the lactobacilli and certain non hæmolytic streptococci but the factors involved the teeth themselves the saliva the food the organisms have complex interactions and so far no convincing theory has been put forward which will explain all the facts

Since some native races and other isolated communities living on natural foodstuffs suffer far less from caries than civilised races it would appear to be fairly certain that our more artificial foods particularly highly refined flour and sugar are an important factor in the production of caries Most plans of prophylaxis are based on this natural food hypothesis although Mellanby believes in the importance of vitamin D

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CHAPTER II-A

VIRUSES AS AGENTS OF HUMAN DISEASE

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If it can be shown conclusively that caries can be prevented largely by restricting our diet to natural foodstuffs it will be an interesting struggle against the now firmly fixed tastes of the civilised races and the vested interests of the millers and confectioners

BIBLIOGRAPHY

It is impossible in a review such as this to give a list of references to articles which cover adequately the subjects touched upon The reader is referred to the excellent standard textbooks available notably The Principles of Bacteriology and Immunity by Topley and Wilson published by Edward Arnold & Co Textbook of Bacteriology by Zinsser and Bayne Jones published by D Appleton Century Co Immunity by Zinsser Enders and Fothergill published by the Macmillan Co

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of trachoma psittacosis and lymphogranuloma inguinale are rickettsiae or viruses In the present state of knowledge it seems advisable to consider all these agents of disease together mainly because similar technical methods are required for their experimental study In all probability the group contains agents of diverse evolutionary origin but very little serious attempt at classification into sub groups has been made

Physicochemical Characteristics of the Viruses

In the last ten years valuable experimental methods have been developed for the study of viruses by physicochemical techniques These include photography by ultraviolet light which allows a higher effective magnification than visible light and in the last year or two photographs of viruses by the electron microscope have been published The resolving power of this instrument is theoretically far greater than any optical microscope but the technical difficulties in obtaining useful pictures of biological material are very great and it is unlikely to do more than confirm the data about viruses which have been obtained by other methods Of these the most useful have been the graded collodion filters of Elford and the various types of ultracentrifuge the use of which is due almost entirely to Svedberg and his school By elaborations of these methods it has been possible to determine the size and approximate shape and density of all those viruses which can be studied conveniently in the laboratory Table I gives the approximate diameter of the infective particles of a number of the viruses of human disease

TABLE I

Sizes of Some Viruses Causing Human Disease

Virus	*Diameter in mμ*
Rickettsiae	500 × 200
Psittacosis	275
Smallpox and vaccinia	175
Rabies	125
Influenza	120
Lymphocytic choriomeningitis	60
Yellow fever	22
Poliomyelitis	12

$1\ m\mu = 1/1\ 000\ 000\ mm$

The density of the virus particles is inversely related to their size the larger ones having about the same specific gravity as bacteria (1 16) the

smaller ones approaching the higher value characteristic of proteins (about 1 3) As far as they have been investigated the viruses responsible for human and animal disease are composed of approximately spherical particles but several of the viruses of plant diseases take the form of slender rods that of tobacco mosaic virus for instance being a cylinder 12 mμ in diameter and about 400 mμ in length

Chemically all viruses seem to be essentially nucleoprotein with in the case of the only large virus so studied vaccinia a certain amount of carbohydrate and fat The most elaborate chemical work has been done with the plant viruses particularly that of tobacco mosaic There is no serious technical difficulty in obtaining several grammes of actual virus substance from diseased tobacco plants so that detailed chemical and physical studies can be made Tobacco mosaic virus is a giant molecule apparently built up of a series of nucleoprotein units arranged in linear fashion These giant molecules are of constant composition give a characteristic x ray diffraction pattern have a density equivalent to that of protein molecules and show no evidence of metabolism It is therefore justifiable to regard them as molecules i e as stable atomic configurations rather than as living microorganisms in the ordinary sense The slender rods of tobacco mosaic virus readily aggregate in partially crystalline form but this characteristic is of no great value in establishing the purity of the material or providing final evidence of its non living character

A great deal of discussion has centred around this material some writers contending that it has shown that certain viruses at least are not microorganisms at all but represent a new category of organization self multiplying enzymes intermediate between protein molecules and micro organisms It is obvious that the isolation of these virus proteins has made even more indeterminate the boundary between living and not living material It should be recognized however that although certain protein molecules have been shown to be of relatively simple and symmetrical structure no real advance has been made in elucidating their mode of synthesis in the living cell It seems to the writer more probable that studies on tobacco mosaic virus and similar simple self reproducing agents will throw light on the nature of the processes by which proteins are synthesized in vivo than that protein chemistry in its present state will provide an explanation of the behaviour of these virus proteins

Biological Characteristics of the Viruses

From the point of view of the clinician the pathologist and the public health worker there are two characteristics of the viruses which are of

primary importance These are first that viruses like all living organisms arise only from preexistent virus of the same type This does not preclude the possibility of changes in virus activity but it does express the fact that virus diseases do not arise spontaneously All the recent discussion about viruses as crystalline proteins is liable to suggest that new proteins of this type and hence new virus diseases might arise with some frequency In practice however it is found that quarantine measures are as effective against virus diseases as they are against any other type of infection There is no evidence whatever that virus species arise by any other processes than those common to all living organisms Some viruses e g that of influenza are intrinsically more variable than others but with all of them changes in their environment such as transfer to a new host species may lead to the selective survival of a variant differing considerably from the parent strain In this way what appear to be new virus diseases arise from time to time but it must be stressed that there is no more evidence for the spontaneous generation of viruses than there is for the generation of putrefactive bacteria from sterile meat infusions or of mice from the Nile mud

The second primary characteristic is the limitation of viruses to one specialized environment they can multiply only within living susceptible cells of suitable host species This limitation is of significance in several directions In the first place it determines the technique by which virus diseases have to be studied In bacteriology proper solid and liquid culture media are used both for the growth of the microorganism being studied and for determining its presence and amount in any given material In virus work culture media have to be replaced by living susceptible cells for both these purposes Most commonly the presence of virus is demonstrated by the inoculation of material which may need to be rendered free of bacteria by filtration into some suitable laboratory animal If the virus is present the animal will show characteristic symptoms and lesions after a certain incubation period The three most useful experimental animals are the mouse the chick embryo and the rhesus monkey Of the twenty human diseases due to viruses there are only three or four which cannot be transmitted to one or more of these species The monkey is susceptible to eleven viruses and irregularly to two more measles and trachoma nine have been transferred to mice and eleven produce lesions on the chorio allantois of the developing chick embryo

For the preparation of virus containing material such as may be required for experimental work or active immunization animal inoculation inoculation on the chorio allantois of the chick embryo or tissue culture

may be used. The last two methods have the advantage that the virus obtained is free from bacterial contamination.

The next implication is that infection by a virus can be contracted only from another infected individual, usually but by no means always of the same species. There are no viruses, for instance, which can alternate between a normal saprophytic life and occasional parasitism in the way many of the anaerobic bacteria do. Virus infections in human beings will therefore result usually from (1) close association with a patient or carrier, the infection being transferred by the respiratory route; (2) direct contact with infectious material as in the venereally transmitted lymphogranuloma inguinale; or (3) transfer from an infected patient or animal by way of an insect vector. Infection by milk, food or water is almost unknown and can occur only in most unusual circumstances. There are one or two poliomyelitis epidemics in which circumstantial evidence of spread by milk has been brought forward, but since the virus cannot multiply in the milk, such an outbreak could only be a result of extremely gross contamination by a carrier actively liberating the virus. It is interesting that there are no known virus infections primarily involving the gastrointestinal tract. This is perhaps to be related to the inability of viruses to multiply in any ordinary foodstuff plus the destructive effect of the gastric acidity on any virus ingested.

The intracellular mode of life probably is responsible also for certain immunological characteristics of virus infections, but these differ so much from one type of infection to another that it is impossible to generalize.

The Evolution of the Viruses

It is perhaps no more than an academic exercise in speculation to discuss the probable evolutionary history of the viruses, but there must always be a certain interest attaching to the status of these agents which seem to be on the border line between the living and the not living. There are three ways of looking at the problem of the general nature of viruses. The most fundamental would be to obtain a full physicochemical description of the virus particles, but as no such description is yet available even for the simplest protein, we must discard this point of view at once. The second way of approaching the problem is the pragmatic one. How are we to consider viruses from the point of view of dealing with them experimentally in the laboratory or of preventing or treating the diseases to which they give rise? The answer to this question is definite and unanimous. Viruses must be treated as if they were living organisms which can be derived only from similar preexisting organisms. The virus

of yellow fever is of just about the same size as a molecule of the protein hæmocyanin but no epidemiologist would consider for a moment that a case of yellow fever could occur in tropical Asia or Australia except as a result of infection by virus brought from one of the endemic regions

The third approach is to consider the probable evolution of the viruses Since palæontological evidence is out of the question discussion can only be based on consideration of the relationships between the different types of extant viruses and of their resemblances to and points of difference from accepted microorganisms on the one hand and protein molecules on the other Such consideration has led to a fairly widespread but by no means unanimous opinion that the viruses responsible for animal disease are best regarded as specialized descendants of larger parasitic micro-organisms This view provides in our opinion a satisfactory coordination of the facts that are available and brings the phenomena of virus disease into intelligible relationship with those of the infections due to bacteria and protozoa

The adoption of a wholly parasitic existence by a living organism usually results in an atrophy or loss of those functions which are no longer required for survival in the new environment Amongst the bacteria it is a general rule that the most highly pathogenic forms are those most difficult to grow on artificial media Their adaptation to parasitic life has been associated with a loss of the power to synthesize their substance from comparatively simple materials

The rickettsiæ are small organisms of bacillary appearance which can be regarded as bacteria which have reached a further stage in the process of parasitic degeneration They cannot be cultured in any bacteriological medium of ordinary type but grow readily in suitable tissue cultures There is evidence that the growth of rickettsiæ takes place predominantly when the tissue cells in the culture are no longer actually living and it seems probable that a close study of rickettsial growth requirements may lead to the production of a non cellular medium in which they can be grown In nature however they have like the true viruses a strictly intracellular habitat

The next stage may be exemplified by the virus of psittacosis The infective particles of this virus are relatively large and when stained can be seen easily with an oil immersion lens their staining qualities are similar to those of the rickettsiæ and bacteria Psittacosis virus can be grown readily in tissue culture and like all the true viruses multiplies in such cultures only so long as the tissue cells remain viable and show an active metabolism This provides a sharply differentiating criterion for separating rickettsiæ from the true viruses There are three other viruses

which resemble psittacosis virus in size and to some extent in staining reactions those responsible for trachoma inclusion blennorrhoea and lymphogranuloma inguinale The last named however approaches in several characteristics a typical virus like vaccinia Table I which could be greatly extended by the inclusion of viruses pathogenic for other organisms than man shows that there is an almost continuous range of size from the largest to the most minute The smallest viruses which in effect are little more than single molecules of nucleoprotein can be regarded as *the ultimate stage to which parasitic degeneration can attain all the* normal attributes of a living organism having been lost with the exception of the power of self multiplication

It must not of course be assumed that all viruses are derived from a common bacterial ancestor There are several red cell parasites of lower animals which appear to be intermediate in character between protozoa and viruses and it is at least as likely that rabies and yellow fever viruses are of remote protozoal ancestry as that they are derived from degenerate bacteria A good case might also be made for regarding the organisms which are like those responsible for pleuropneumonia of cattle as degenerate fungi which have almost reached the level of the true viruses

The alternative hypotheses in regard to the evolution of the viruses *may be stated as (1) that they represent residual examples of the earliest* pre cellular stages of organic evolution (2) that they are derivatives of metazoan organisms representing portions of the reproductive apparatus possibly genes which have taken on anarchic pathogenic activity It is possible to present a case for either of these views but neither provides a lead for experimental studies or throws any light on the obvious resemblances between bacteria and viruses

The Main Types of Human Virus Infections

Virus infections are almost as multiform in their manifestations as those due to bacteria and it is quite impossible to generalize on such matters as the route of infection the persistence of the virus in the body *and the duration of immunity unless we divide the viruses responsible* for human infections into a number of separate groups If we do this a certain degree of uniformity can be observed within each group Unfortunately a number of the most important virus diseases of man cannot be studied in detail for want of a suitable experimental animal and discussion of their behavior necessarily must be mainly from analogy to those which can develop in some experimental animal

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epidemiological grounds The experience of the Faroe Islands in regard to measles provides a classical example of a community in which measles remained absent for many years after a widespread epidemic in 1781 If those infected at that time had remained latent carriers of the virus it is inconceivable that no outbreak should occur till the fresh introduction of the disease from Denmark sixty five years later Experience indicates that once a patient has recovered completely the virus has been destroyed and there is no danger of his infecting susceptible individuals

Group 2

Virus Infections Conveyed by Insects or Other Arthropods

If we omit the rickettsial infections virus diseases of this group must be subdivided into two subgroups (*a*) yellow fever dengue fever and some rarer diseases such as Rift Valley fever and sand fly fever in which the symptoms are of a general somatic infection with damage to the liver often a predominant feature and (*b*) the human types of virus encephalitis including those due to the St Louis encephalitis virus Japanese encephalitis B virus and equine encephalomyelitis virus

(*a*) Yellow fever is the only disease of this sub group which has been studied in detail but the others probably are of similar type though usually less severe The virus of yellow fever is introduced into the body by mosquito bite and multiplies mainly in the liver but possibly also in other tissues in immediate contact with the blood stream At the height of the disease enormous numbers of virus particles up to 10^{10} per c c are present in the blood If death does not occur antibody appears early and a few days after the onset of symptoms the blood becomes non infective The antigenic stimulus provided by the infection is a very powerful one and immunity and antibody persist indefinitely

There are records of individuals who suffered from yellow fever sixty years previously and still possessed easily demonstrable antibody although they had not been in an endemic region in the interim Urban yellow fever is a strictly human disease the virus being conveyed from patient to patient by the mosquito *Ædes ægypti* In tropical South America and possibly in Central Africa alternate hosts of the virus exist in the indigenous monkeys and other types of mosquito than *Ædes* are responsible for human infections

(*b*) The several types of virus encephalitis mentioned probably are all transmitted by mosquitoes but final proof by the isolation of the virus from naturally infected mosquitoes has not yet been given There is a

Group 1

The Exanthemata Including Smallpox Measles Chickenpox and Possibly Rubella and Mumps

These are virus infections spread by the respiratory route highly specific for the human species having a long twelve to fourteen days incubation period followed by an acute onset of symptoms and giving rise as a rule to life long immunity The long incubation period of these diseases has never been explained adequately It seems clear that the virus enters the body by the upper respiratory tract and multiplies during the incubation period without producing symptoms At the time of onset of symptoms there is almost certainly an acute liberation of virus into the blood and the characteristic skin lesions must be due to the focal multiplication of virus brought by the blood stream It has been suggested that allergic factors are concerned in the process A reasonable hypothesis might be that virus entering the blood from the presumptive initial lesion is taken up predominantly by reticuloendothelial cells Sensitizing antibody is produced by these which passes to and is taken up by the capillaries in the skin and elsewhere When a certain stage is reached the co existence of antigen virus and antibody in the body results in an acute reaction analogous to serum sickness but with the complication that the primarily allergic reactions in the skin and mucous membranes form points of weakness which can be occupied by circulating virus and allow its further multiplication In the writer s opinion some such mechanism probably is involved in producing the characteristic form of these diseases but it must be stressed that there is no direct experimental evidence whatever to support the opinion It is unfortunate from one point of view that typical smallpox does not often occur in the cities possessing fully equipped virus laboratories a detailed study of the quantity of virus in the blood at different stages of the disease probably would throw much light on the whole problem of these diseases

The life long immunity which usually follows an attack of any of these viruses probably can be related to the fact that at one or possibly more stages of the disease there are large amounts of virus in the blood This is taken up by reticuloendothelial cells all over the body and provides therefore an intense antigenic stimulus the effect of which persists almost indefinitely There are some who think that long lasting immunity is only possible when recurrent antigenic stimuli are received and such writers would postulate that in these diseases the virus persists in the body for life General opinion is strongly opposed to this view mainly on epi

Group 4

Superficial Infections of the Respiratory and Pharyngeal Mucous Membranes

Epidemic influenza is the chief example of this group but there are probably numerous other viruses responsible for colds and the various febrile catarrhs from which influenza virus cannot be isolated In the opinion of the writer poliomyelitis virus should be included also in this group

In experimental animals influenza virus can infect only the epithelium of the respiratory tract and there is no reason to believe that it has any wider potentialities in the human being An attack of influenza probably is the result of a spreading superficial infection of the nasal tracheal and bronchial mucosa with the virus Involvement of the actual lung substance either occurs rarely or does not result usually in clinically detectable changes Uncomplicated influenza has a short incubation period of two to three days and acute symptoms last only a few days Following recovery there is always an increase in the amount of circulating antibody capable of neutralizing the virus and since second attacks do not often occur in one epidemic a certain degree of immunity results Immunity to influenza is however by no means so clear cut as immunity to measles or yellow fever The level of serum antibody has in our experience had very little effect in determining whether or not a person exposed to infection will contract the disease Subclinical attacks during an epidemic are quite common the only evidence of infection being a rise in the serum antibody

It is possible that future work will provide means for the isolation and study of other viruses which produce human respiratory infections As far as can be seen at present however true epidemic influenza is the only one for which there is any possibility of developing immunological methods of control or treatment By laboratory workers this disease would be defined as one resulting from infection by a virus capable of producing the characteristic infection of the ferret and inducing in the patient an increase in neutralizing antibody against a known strain of influenza virus It is not possible with certainty to diagnose a case of true influenza on purely clinical grounds However it appears justifiable to state that if an epidemic of respiratory infection shows certain epidemiological and clinical characters the chances are about ten to one that it is true influenza The epidemiological requirements are (1) the epidemic appears suddenly often in association with a spell of cold weather (2) it involves a high proportion of the population 10 per cent or more (3) it lasts

good deal of indirect evidence that these viruses first multiply in somatic tissues and liberate virus into the blood Infection of the central nervous system is not invariable and in some epidemics may follow only a small proportion of somatic infections In experimental animals it is common for viruses of this group to reach the central nervous system from the blood by way of the olfactory mucous membrane but there is no evidence as to whether this occurs in human beings and other ways by which the central nervous system can be infected are equally conceivable The epidemiology of the diseases points strongly to the existence of an animal reservoir in each instance but only that of equine encephalomyelitis has been demonstrated experimentally The Eastern type of this virus apparently is a natural parasite of certain wild birds infection both of horses and of human beings is only accidental Immunity probably is substantial but all the diseases are rare and there is insufficient experience available to allow a definite statement The disease encephalitis lethargica probably is not a member of this group its etiology being still quite unknown

Group 3

Rabies

Rabies hydrophobia is unique in its pathology being probably the only virus whose neurotropism is a specific adaptation to allow its continued survival It is the neurotropic virus par excellence there being no evidence of its ability to multiply in any non nervous tissue with the one possible exception of the epithelium of the rabbit cornea It is introduced into the body through the bite usually of a rabid dog in Trinidad and possibly on the South American continent infection may occur through the bite of the vampire bat *Desmodus* The virus passes along the nerves to reach the central nervous system and by its multiplication particularly in the medulla produces the characteristic symptoms of the disease From the central nervous system the virus spreads centrifugally through all types of nerves and in the dog etc reaches the various subepithelial collections of nerve cells in the mouth A rabid dog invariably shows small traumatic lesions of the buccal mucosa and it is probably through these that the virus is liberated into the saliva There are probably still some aspects of the natural history of rabies to be worked out and from analogy with other virus diseases it seems rather likely that a reservoir of infection will be found eventually in some wild mammal which normally suffers only subclinical infection

peculiar type of degeneration and liquefaction occurs. In most respects it can be regarded as suppuration in which the pyogenic bacteria are replaced by the virus. In females the pelvic lymph glands are involved usually, and low grade inflammatory changes spread to the perirectal tissues, often resulting eventually in stricture of the rectum. The slow development of pelvic lesions and the relatively long periods that the virus remains present in the tissues of some experimental animals suggest that the virus is only very slowly eliminated from the body and that immunity reactions usually are ineffective.

There can now be no doubt that trachoma is a virus disease; the only remaining controversy is whether the responsible microorganism should be classed as a rickettsia or a true virus. The evidence on the whole is strongly in favour of the view that the Halberstaedter Prowazek elementary bodies are virus particles of the same general character as those of psittacosis virus. The virus is a large one, about 250 mμ in diameter in its standard form but again like psittacosis virus also taking the form of larger units, the initial bodies of Lindner. As is well known the disease is an extremely persistent one, and although the virus is not demonstrated so readily in long standing lesions it certainly is still present. Immunity reactions appear to be ineffective.

Inclusion blennorrhœa is another disease of the conjunctiva due to a virus morphologically similar to that of trachoma but developing more rapidly and clearing up within a short period without the serious sequelæ of trachoma. It can be regarded as a virus closely related to trachoma virus but not yet so thoroughly adapted to its environment. The local inflammatory and immunity responses of the body are sufficient to eliminate the less adapted virus but are quite inadequate in most of those infected with trachoma.

We may summarize the characters of this group of viruses producing localized lesions as showing an almost continuous range of activity from inclusion blennorrhœa, which is an acute self limited infection, through psittacosis, lymphogranuloma inguinale to trachoma and the indolent skin affections molluscum contagiosum and warts, in which there is a long persistence of the virus and a very ineffective immunity response.

Group 6

Herpes Simplex

Although a typical virus can be isolated readily from vesicles of ordinary febrile herpes, certain authors have considered that the infective

poliomyelitis is however so complicated and controversial that it would be out of place to attempt any general account of the position here

Group 5

Localized Virus Infections

None of the virus diseases which have been considered above produce localized lesions some produce multiple focal lesions as a result of spread by the blood but all can be regarded as generalized infections of one or more groups of tissues There remain for consideration those virus diseases which produce lesions localized to the point of primary infection or reaching other parts of the body only by mechanical means The viruses which can be included in this group are those of psittacosis lymphogranuloma inguinale trachoma molluscum contagiosum and warts Only the first three of these have been studied adequately and we shall omit any discussion of molluscum and warts All three viruses are composed of relatively large particles visible with ordinary microscopic technique and staining in similar fashion to rickettsiae and bacteria If the view that viruses are derived from bacteria by a process of parasitic degeneration is correct then those of this group represent an early stage in the evolution Their pathogenic activity also is more allied to that of bacteria than that of the more typical viruses

Psittacosis in man is always an inhalation pneumonia resulting from breathing air contaminated with dust from infected parrots or other birds Subcutaneous injection of living virus does not produce psittacosis Clinical psittacosis is so rare in children and young adults that one can be reasonably certain that when such individuals inhale psittacosis virus only trivial self limited lesions are as a rule produced in the lung In older people the lesions may spread in bronchopneumonic fashion producing severe or fatal illness When recovery occurs the lesions heal slowly and virus can be detected in the sputum for about three weeks from the onset of symptoms The disease is too rare to allow a statement as to the extent or duration of immunity There is at least one instance on record of a second infection in a laboratory worker two years after the first In naturally infected parrots and in experimentally infected mice the virus may remain present in the spleen for long periods during which the bird or animal shows no symptoms

Lymphogranuloma inguinale is a venereal disease with an insignificant papulovesicular primary lesion on the skin or genital mucous membranes The clinically obvious lesions are in the associated lymph nodes where a

cal entities The viruses that have been discussed are only the survivors of a host of forms of varied evolutionary history Some of them clearly have evolved as parasites of other hosts than man and if the hypothesis that viruses are descendants of larger microorganisms is correct it is quite possible that many different species may have served as hosts at various stages in the evolutionary transformation that has given rise to a present day virus In the circumstances one must expect to find forms which appear to be without relationship to any other forms which appear to be intermediate between well-defined groups and others which at different times or in different host species show quite distinct types of behaviour To take a few examples psittacosis in its natural host the wild parrots is not a disease of the lungs but a generalized infection with chronic localization of the virus in spleen and kidney after clinical recovery Only in human beings could it be regarded as essentially a local disease Chicken pox has been grouped with the other exanthemata but this is clearly no place for the closely related or identical virus of herpes zoster Yellow fever again has two distinct natural modes of spread corresponding to the urban and jungle types both utilizing a mosquito vector yet laboratory experiments and mishaps indicate that under rare conditions it may be transmitted by contact of infective blood and unbroken skin or in monkeys by ingestion of the virus

The Production of Symptoms in Virus Diseases

It is usual to ascribe the pathological changes and general symptoms resulting from bacterial infections to the liberation of toxic substances from the bacteria These may be either exotoxins liberated from intact bacteria or endotoxins set free by solution of dead bacterial bodies There is no evidence that viruses produce either of these types of toxin and some other explanation is required to account for the symptoms produced by virus infection

The most reasonable approach to the problem is to consider the processes which must be involved to allow the intracellular multiplication of a virus We have adopted already the point of view that viruses represent the degenerated descendants of pathogenic microorganisms The loss of the power of growth outside of the living cell would than be interpreted as a loss of those enzymes which change or activate food molecules into a form in which they can be built up into the living structure of the microorganism In the absence of these enzymes the virus is forced to utilize the activated molecules which are constantly present within the living host cell as a result of its varied intracellular enzyme activities

agent should be regarded as an endogenous product of physiologically stimulated human cells rather than an independent microorganism. During 1938 we undertook an extensive study of human sera to determine what proportion of individuals of various ages and of different social grades gave evidence of being infected with the virus. At the same time investigations on aphthous stomatitis of children confirmed previous American work that this condition was due usually to infection with herpes virus. The conclusions we reached have not yet been accepted generally but they appear to be consistent with the results of other investigators in the same field and will be adopted here. According to this view, primary infection with herpes nearly always takes the form of aphthous stomatitis and occurs almost entirely during infancy, i.e. under the age of three years. The infection often is associated with definite fever and general symptoms, but it is probable that subclinical primary infections also occur. A much higher proportion of children in the public hospital class become infected than amongst those from more comfortable homes. In Melbourne over 90 per cent. of public hospital patients are infected as compared with around 40 per cent. of middle class individuals. If infection fails to occur in infancy the child develops a nonspecific resistance which, under ordinary circumstances, results in its remaining permanently free from infection. Those who are infected in infancy overcome the immediate infection in a week or ten days, but the virus remains permanently implanted in the tissues and at any time throughout life may be called into activity by the appropriate stimulus. Any human population may therefore be divided sharply into two groups: herpetics permanently infected with the virus and non-herpetics. Herpetics alone are subject to attacks of labial herpes, the intensity of the stimulus necessary to provoke an outcrop varying greatly from individual to individual; all possess relatively large amounts of antibody capable of inactivating the virus in vitro. Non-herpetics never show labial herpes, no matter how intense the febrile stimulus to which they are exposed, and their serum contains no antibody.

From one point of view herpes virus may be regarded as having reached that type of equilibrium with its host toward which all viruses are in some sense striving. It persists indefinitely despite the development of circulating antibody, does no serious damage to its host, and by recurrent outbursts of activity ensures the periodic liberation of virus into the environment and the infection of fresh susceptible individuals.

It will have been evident that this attempt to classify the virus diseases meets with the difficulties that confront any classification of biolog-

cal entities The viruses that have been discussed are only the survivors of a host of forms of varied evolutionary history Some of them clearly have evolved as parasites of other hosts than man and if the hypothesis that viruses are descendants of larger microorganisms is correct it is quite possible that many different species may have served as hosts at various stages in the evolutionary transformation that has given rise to a present day virus In the circumstances one must expect to find forms which appear to be without relationship to any other forms which appear to be intermediate between well-defined groups and others which at different times or in different host species show quite distinct types of behaviour To take a few examples psittacosis in its natural host the wild parrots is not a disease of the lungs but a generalized infection with chronic localization of the virus in spleen and kidney after clinical recovery Only in human beings could it be regarded as essentially a local disease Chicken pox has been grouped with the other exanthemata but this is clearly no place for the closely related or identical virus of herpes zoster Yellow fever again has two distinct natural modes of spread corresponding to the urban and jungle types both utilizing a mosquito vector yet laboratory experiments and mishaps indicate that under rare conditions it may be transmitted by contact of infective blood and unbroken skin or in monkeys by ingestion of the virus

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This abstraction of activated molecules by the multiplying parasite naturally will disorganize intracellular processes and cause the liberation of abnormal metabolites

In very general terms the result of these changes is first to stimulate the proliferation of adjacent cells particularly epithelium and second to cause progressive degeneration and eventual necrosis of infected cells Depending on the intensity of the intracellular changes virus lesions may show anything from purely proliferative changes as in warts to acute necrosis such as is seen in the liver of a fatal case of yellow fever The most typical lesion however is probably the "pock" in which both proliferative and necrotic processes are equally evident Wherever necrosis occurs there is an adjacent inflammatory reaction acute or sub acute according to the intensity of the necrosis This must be regarded also as a result of the diffusion of abnormal metabolites from cells damaged by virus multiplication rather than to the effect of hypothetical virus toxins The general toxic symptoms presumably are of similar origin

The Part Played by Bacteria in Virus Diseases

In view of the ubiquity of potentially pathogenic bacteria particularly in the upper respiratory tract it is only to be expected that certain virus infections will provide an opportunity for secondary bacterial invasion which clinically may be more important than the primary virus infection The middle ear infections and bronchopneumonias which so frequently follow measles are typical examples The influenzal infections are especially prone to be associated with or followed by bacterial infections of the respiratory tract It seems highly probable that certain influenza epidemics are due to the associated activity of virus and Pfeiffer s bacillus This opinion must be based at present largely on analogy with the conditions in swine influenza a disease in which the conjoint action of an influenza virus and a hæmophilic bacillus are necessary for the production of symptoms In recent epidemics there has been little evidence that bacteria played any significant part in producing the primary infection No pandemics of severe influenza have however occurred since methods of studying the virus have been available and it is still possible that the severity of the great pandemics was due rather to the associated bacteria than to the virus A majority of the fatal cases of the 1918–19 pandemic in which postmortem bacteriological investigations were made showed Pfeiffer s bacillus or a hæmolytic streptococcus in the hæmorrhagic lung lesions

Smallpox is another virus disease in which bacterial infection is an essential featu e of the severe disease Fatal smallpox probably is always a result of streptococcal infection which involves both the skin lesions and those of the mucous membranes

Immunity to Virus Diseases

In de cribing the different types of human virus diseases we have in dicated what a wide disparity there is in the effectiveness of the im munity which follows a natural attack of virus disease It is clearly impossible to make any such generalization as that immunity following virus diseases is more permanent and complete than that which follows bacterial infections

There has been much controversy as to the mechanisms involved in virus immunity and a good deal of the apparent difficulty of the subject may be traced to a failure to perceive how different the pathology of different virus infections may be On the whole there is a general ten dency to belittle the importance of antibody production and to postulate tissue immunity as the most important factor in determining post infection immunity It is obviously impossible to discuss the pros and cons of the problem here and we can only pre ent in the space at our disposal a rather dogmatic statement of one likely interpretation of the facts

In order to obtain permanent immunity it is necessary first that an intense stimulus be applied to the antibody producing mechanism of the body so that the capacity to produce antibody is retained for years and second that the viru which might produce reinfection meets circulating antibody and/or specifically modified inflammatory cells before it has an opportunity to reach those cells in which it can multiply sufficiently to produce symptoms These requirements are only completely fulfilled in such diseases as smallpox measles and yellow fever All of these show at some period a high concentration of viru in the blood which must pro vide an energetic stimulus to the reticuloendothelial system Further in each case we mu t assume that before symptoms appear the virus is transported in the blood to those organs in which symptom producing lesions occur The presence of circulating antibody should therefore provide an effective protection against symptomatic infection The only exceptions to this rule appear to be dengue and pappataci fevers in which immunity after an attack appears to last only from six months to two years There is insufficient experimental work with these diseases on record to allow any explanation of the discrepancy In other virus dis

cases one or other of these requirements remains unfulfilled The superficial virus infections of mucous membranes like influenza usually result in superficial necrosis and antigenic material can pass to the local lymph nodes and possibly to other parts of the reticuloendothelial system to provoke an antibody response With regeneration of the infected epithelium a non receptive state is established temporarily which may perhaps in the case of influenza be due to the incomplete differentiation of the regenerated cells into typical respiratory epithelium Immunity in experimental animals however persists after the epithelium has been completely regenerated and its degree is fairly closely correlated with the amount of antibody in the circulating blood Ferrets or human beings may be susceptible to infection at a time when they possess considerable amounts of antibody probably because infection of the mucosa can occur directly from the environment and unless the initial focus of infection is dealt with the virus can spread superficially over an extensive area of susceptible epithelium

In poliomyelitis the problem of immunity is complicated by the fact that the clinically recognizable form of the disease can be regarded as on the whole a rather rare complication of infection There is a great divergence of opinion as to the part played by specific immunity in shaping the epidemiology of the disease A good case can be made out for the view that subclinical infection with the virus results in an increase in resistance to paralytic infection but does not render the individual immune to further nonparalytic infections The significance of antibody against poliomyelitis virus is particularly obscure its presence is certainly not a guarantee of immunity to paralysis and it is not usually produced after a paralytic infection

At the opposite end of the scale from the exanthemata we have herpes simplex infection which is almost wholly uninfluenced by the presence of large amounts of circulating antibody The essence of this infection is the persistence of the virus in the body recrudescent activity is not a result of re infection but apparently results from some physiological stimulus which allows latent virus which has remained in the body to develop local pathogenic activity Under normal conditions the virus seems capable of existing in a symbiotic relationship with the cell but under the influence of changes possibly of nervous origin (compare with herpes zoster) the balance is destroyed and the virus multiplies and produces cell damage and necrosis of the usual type The circulating antibody may have some effect in limiting the extent of the recrudescent lesions but it is clear that it has no capacity whatever to eliminate the residual quiescent infection

ARTIFICIAL IMMUNIZATION AGAINST VIRUS DISEASES

It is a general rule that one cannot hope to induce by artificial immunization an immunity more effective than that which follows recovery from an attack of the disease in question Within these limitations the problem of immunization against virus diseases is theoretically simple All that is needed is to arrange that the antibody producing mechanisms of the body are stimulated by an *adequate amount* of virus antigen which retains its *normal antigenic character* In practice however it is often very difficult to imitate the process of bacterial vaccination first because of the technical difficulty of obtaining large amounts of virus and second because of the damage to many virus antigens which follows their inactivation by heat or antiseptics

Most virus preparations must of necessity consist of a tissue extract containing several grammes of host protein for each milligramme of actual virus In one or two animal diseases notably equine encephalomyelitis crude virus extracts inactivated by formalin have proved effective vaccinating agents but no undoubted successes by such methods have been recorded for human virus diseases In the future it may be possible to produce by the use of the ultracentrifuge large amounts of purified virus free from tissue proteins Such material suitably inactivated may eventually prove to be the most safe and effective type of virus vaccine but the expense and technical difficulties have prohibited so far its practical development

All the successful current methods of immunization depend on the inoculation of living virus whose activity has been suitably attenuated Jennerian vaccination is the classical example Vaccination against yellow fever depends on exactly similar principles By passage of the virus through alien hosts first the mouse and then the tissues of embryo chicks its virulence for man has been greatly reduced without significant change in antigenic character Subcutaneous injection gives rise to a multiplication of the virus often with mild symptoms and an effective antigenic stimulus is applied Methods of this sort are by no means ideal the virus is a labile object and great care may be required to retain the immunizing strain at a suitable degree of virulence If it should revert to the virulent form a large scale catastrophe may result but if the virulence becomes negligible insufficient virus may be generated in the body to stimulate adequate antibody formation

Another principle has been adopted in some experimental attempts to immunize against infections naturally limited to some particular group of tissues Psittacosis in man is a disease only of the lungs Inoculated

cases one or other of these requirements remains unfulfilled. The superficial virus infections of mucous membranes like influenza usually result in superficial necrosis and antigenic material can pass to the local lymph nodes and possibly to other parts of the reticuloendothelial system to provoke an antibody response. With regeneration of the infected epithelium a non receptive state is established temporarily, which may perhaps in the case of influenza be due to the incomplete differentiation of the regenerated cells into typical respiratory epithelium. Immunity in experimental animals, however, persists after the epithelium has been completely regenerated and its degree is fairly closely correlated with the amount of antibody in the circulating blood. Ferrets or human beings may be susceptible to infection at a time when they possess considerable amounts of antibody, probably because infection of the mucosa can occur directly from the environment and unless the initial focus of infection is dealt with the virus can spread superficially over an extensive area of susceptible epithelium.

In poliomyelitis the problem of immunity is complicated by the fact that the clinically recognizable form of the disease can be regarded as on the whole a rather rare complication of infection. There is a great divergence of opinion as to the part played by specific immunity in shaping the epidemiology of the disease. A good case can be made out for the view that subclinical infection with the virus results in an increase in resistance to paralytic infection but does not render the individual immune to further nonparalytic infections. The significance of antibody against poliomyelitis virus is particularly obscure: its presence is certainly not a guarantee of immunity to paralysis and it is not usually produced after a paralytic infection.

At the opposite end of the scale from the exanthemata we have herpes simplex infection which is almost wholly uninfluenced by the presence of large amounts of circulating antibody. The essence of this infection is the persistence of the virus in the body; recrudescent activity is not a result of re-infection but apparently results from some physiological stimulus which allows latent virus which has remained in the body to develop local pathogenic activity. Under normal conditions the virus seems capable of existing in a symbiotic relationship with the cell, but under the influence of changes possibly of nervous origin (compare with herpes zoster) the balance is destroyed and the virus multiplies and produces cell damage and necrosis of the usual type. The circulating antibody may have some effect in limiting the extent of the recrudescent lesions but it is clear that it has no capacity whatever to eliminate the residual quiescent infection.

as belonging to the same species Unfortunately such cross immunity experiments have not been carried out with all types and other factors must be considered in attempting a classification These include the type of proteus agglutination which appears in the blood serum during convalescence the animal reservoir of infection and the responsible arthropod vector On the whole clinical criteria are not of much help in differentiating the diseases Apart from differences in the average severity of infection the general symptomatology of them all is very similar There are two types of infection tsutsugamushi and fievre bouttoneuse in which a primary rickettsial lesion of the skin develops but in both instances the rickettsiae responsible are very similar to others giving rise to infections without a primary lesion

In the accompanying table Table II the data in regard to these points are shown and it will be seen that it is possible to divide the rickettsiae pathogenic for man into five species some of which contain fairly well defined sub species There are still a number of tropical fevers due to rickettsiæ in regard to which there is insufficient data to allow their classification and it is rather probable that a complete survey of all the pathogenic rickettsiæ would provide some intermediate forms which would not fall easily into any one of the five species that have been accepted in Table II

Pathology of Rickettsial Infections

Though the severity of the infection may be widely different all the diseases of the group show a general resemblance in pathology and symptoms All are naturally acquired as a result of an inoculation into the tissues by the bite of a blood sucking arthropod There is a general belief that the occurrence or not of a local specific lesion at the site of inoculation is more dependent on the way the inoculation is made than on the character of the rickettsia Experimentally intradermal injections will result usually in specific ulceration and the ulcers in tsutsugamushi and fièvre bouttoneuse may arise either because the usual natural inoculation is an intradermal one or because of associated changes due to toxic substances injected at the same time

The essential pathology of all these infections is similar they are diseases of the small blood vessels However introduced the virus circulates in the blood and lodges in the endothelial cells of the capillaries arterioles and sinusoids of various organs The two human diseases which commonly result in a fatal termination Rocky Mountain spotted fever and typhus show lesions which differ essentially only in minor details of

subcutaneously the living virus produces only an insignificant local lesion but provokes antibody formation In all probability this type of vaccination will protect against the natural infection but the disease is too rare to allow full proof of its effectiveness being obtained This method of immunization by inoculating active virus by an unnatural route has been applied also to influenza and on a commercial scale to protect poultry flocks from infectious laryngotracheitis The obvious danger is that inoculated individuals may become a source of active virus from which others may be infected

RICKETTSIAL INFECTIONS

The rickettsial infections include typhus fever Rocky Mountain spotted fever and a large number of less clearly defined febrile infections particularly of the tropical and subtropical regions In discussing the evolution of the viruses some mention has been made of the rickettsiæ as possibly representing an intermediate stage in the parasitic degeneration of bacteria to viruses They may be defined as small rod shaped micro organisms of intracellular habitat and incapable of growth on artificial media All those which are known to produce human disease are transmitted by arthropod vectors lice fleas ticks or mites and it is generally supposed that they have evolved from bacteria which have taken up a symbiotic existence in arthropods Many insects normally contain cells which are crowded with bacteria and there appears to be a special mechanism by which these bacteria are passed through the egg to the young It is doubtful whether any of these symbiotic bacteria have been grown in artificial culture and as many types are small they might well be regarded as rickettsiæ In all probability the development of pathogenicity for mammals including man by microorganisms of this type is in the nature of a biological accident

It is of great practical importance that following infection with most types of rickettsiæ patients develop agglutinins for one or other of the X strains of *Bacillus proteus* the Weil Felix reaction The reason for this is obscure but it provides an invaluable method of diagnosis and a means of classifying the human rickettsial infections

Classification of the Rickettsiæ

The most natural method of dividing up the pathogenic rickettsiæ into species is on an immunological basis If two strains mutually immunize animals against subsequent infection by the other they must be regarded

intensity and distribution There are certain situations where the vascular endothelium is more susceptible to infection than others In typhus the lesions involve predominantly the skin skeletal muscles and central nervous system with minor changes in heart liver and kidneys In Rocky Mountain spotted fever blood vessels of the skin and male genitalia are those predominantly affected the chief difference from typhus being the almost complete absence of lesions in the central nervous system There have been too few pathological studies of the other diseases of the group to allow any statement as to the distribution of lesions From the similarity of the experimental infections in guinea pigs one can be reasonably certain that in human beings the pathology is similar to that of mild typhus cases

In endothelial cells of susceptible blood vessels the rickettsiae proliferate and eventually cause necrosis of the cells involved with secondary changes whose character depends on the intensity of the necrotic process In typhus fever perivascular accumulation of cells either diffuse or in the form of typhus nodules is the characteristic effect In Rocky Mountain spotted fever necrotic changes and hæmorrhage are more marked and an involvement of the muscle cells of the media of small arteries is almost pathognomonic

Immunity

Following recovery from a definite attack of one of the rickettsial infections there is a long lasting immunity against reinfection by the same type When primary infection occurs during childhood in endemic regions the attack is almost always mild and unless reinforced by further subclinical infections may not produce lifelong immunity

There is a good deal of evidence that recovery from illness may not signify the complete elimination of the virus from the body Zinsser's interpretation of Brill's disease which was described first amongst Polish inhabitants of New York is that it represents a reawakening of the true typhus rickettsia which has persisted in a latent state since a primary infection contracted in Europe often many years previously In all probability the survival of the typhus virus from one season to another in an endemic area like eastern Poland depends on the existence of convalescent carriers

During convalescence the serum of the patient develops antibody capable of agglutinating the specific rickettsia and with the exception of Australian Q fever cases of agglutinating one or other form of *B proteus* X It is still not clear as to what is the relationship between the rickett

TABLE II

THE RICKETTSIAL INFECTIONS OF MAN

Disease	*Reservoir*	*Vector*	*Proteus agglutination*	*Immunological type*	*Local lesion*	*Geographical distribution*	*Rickettsia*
Classical typhus	Man	Louse	X 19+++	A	–	Eastern Europe, Northern Africa, South Africa, North and Eastern Asia, Central and South America	*R. prowazeki* (da Rocha Lima)
Endemic typhus	Rat	Flea	X 19+++	A	–	Cosmopolitan	(*R. mooseri*)
Scrub typhus	Rodent	Mites	X K +++	B	–	South-eastern Asia, East Indies, Queensland	*R. orientalis* (Nagayo)
Tsutsugamushi			X K +++	B	+	Japan, Malaya, East Indies	
Rocky Mountain spotted fever	Rodent	Tick	X 19+ X K +	C	–	U.S.A., Brazil (São Paulo)	*R. Rickettsi* (Wolbach)
Fièvre boutonneuse	Dog	Tick	X 19+ X K +	C	+	Mediterranean countries, South Africa (?)	(*R. conori*)
Q Fever	Bandicoot Rodent (?)	Tick	Nil	D	–	Queensland, Montana	*R. burneti* (Derrick)
Trench fever	Man	Louse	?	?	–	Europe 1914–18	*R. quintana* (Töpfer)

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sia and the corresponding proteus strain. The most likely answer is that certain presumably polysaccharide antigens are common to both species of microorganism and that there is no real biological relation between the two. Some workers, however, consider the possibility that the proteus strains are large non-pathogenic variants of the rickettsia.

The antibody which follows infection with rickettsiae differs in one important factor from most virus antibodies. As a rule a mixture of immune serum and a virus like that of influenza which fails to give obvious infection also fails to give immunity to the animal inoculated. In other words the virus is rendered completely non-infective. With rickettsia-immune serum mixtures on the other hand very little or no temperature response may result in the inoculated animal but almost without exception the animal is infected and can be shown to be immune to a subsequent test injection of living rickettsiae.

Prophylactic immunization against the two important rickettsial diseases has been attempted with considerable success. In order to obtain sufficient bulk of antigen it appears necessary to use infected vectors rather than mammalian tissues for the preparation of vaccine. Weigl's typhus vaccine is made from lice infected artificially by anal inoculation while the Montana vaccine against Rocky Mountain spotted fever is prepared from the bodies of infected ticks. Both these vaccines are sterilized by chemical methods and both have been shown to be effective in field trials. In the heavily infected North African countries a good deal of use has been made of a living vaccine derived from a murine typhus strain of low virulence. Only a small proportion of clinically obvious infections result from its use and effective immunity usually results. For mass protection in endemic regions where delousing is impracticable this is probably the most practical method.

Recently Zinsser, Plotz and Enders (Science 1940 XCI 51) have described a method of mass production of vaccine against typhus fever of the European variety consisting of a combination of their agar method and the egg technique as a source of inoculum.

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CHAPTER III

FOCAL INFECTION

By Ernest E. Irons

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Focal infection may be defined broadly as the growth of organisms in a circumscribed tissue and the dissemination of these organisms or their products to distant parts of the body with the production of symptoms or disease. The local infection may be acute or chronic and give clinical evidence of its presence or be symptomless. The acute furuncle from which staphylococcal infection enters the blood stream with resulting osteomyelitis and sepsis or the acute sore throat followed by streptococcal arthritis are called to mind as coming within this definition. In this sense the scope of "focal infection" approaches that of "portal of entry" of infection.

The tendency to broaden the range of focal infection has led some to the consideration under this head of conditions such as pylephlebitis following sup-

purulent appendicitis brain abscess following bronchiectasis and lung abscess, or arterial emboli and petechiae occurring in the course of bacterial endocarditis The mechanism here is that of embolism of infection originating in one focus and proceeding to another but this interpretation is more inclusive than usually is contemplated in the definition of focal infection

Focal infection is here used in the more restricted sense of a local infection, often chronic and symptomless such as an alveolar or peritonsillar abscess occurring in a patient whose symptoms suggest disease or dysfunction of a distant part of the body Removal or cure of the chronic local infection may result in the subsidence or relief of the distant lesions The phrase focal infection unfortunately has been used often as if it represented a disease entity It is better thought of as a concise term to describe a group of factors which include a local infection from which effects are produced in distant parts of the body or which may play a contributory role in accentuating or continuing symptoms of disease in another part of the body

Enthusiasm for a new method of clinical approach, stimulated by occasional brilliant clinical results has however led to generalizations unjustified by a careful weighing of clinical facts It has been assumed for example that because patients with recurrent arthritis have recovered permanently following the discovery and removal of alveolar abscesses or chronic tonsillar infections a similar favorable result will follow the removal of tonsils or teeth in other sufferers from arthritis in whom there may be several etiological factors apart from that of chronic local infection The difficulty here comes through failure to consider the multiple causes of arthritis other than infection, such as trauma, nutritional changes arising from interference with blood supply, hereditary constitutional defects in quality and resistance to injury of joint cartilage, or mechanical factors resulting from muscle imbalance or from fibrous or bony change which continues the disability initiated perhaps by acute or chronic infection In those instances in which chronic local infection is the chief cause of arthritis, the discovery and elimination of the local infection often will result in the cure of the disability In those cases in which other factors are more important, removal of infections may be of some advantage to the patient but cannot be expected alone to effect a cure Similarly in many conditions other than arthritis focal infection may play a part and should be recognized and corrected

Another fact often forgotten in the eagerness of the search for a possible causal local infection is that many persons harbor for years infections such as alveolar abscesses and yet suffer from none of the ills commonly ascribed to focal infection The resistance of tissues and fluids of the host evidently are as important as the infection itself in determining the occurrence of meta

static lesions Emphasis on focal infection to the exclusion of other causes has led to excesses in treatment which have tended to discredit an important therapeutic measure In the evaluation of the clinical effects of removal of chronic infections as in the judging of results of any therapeutic procedure the common pitfalls are failure to maintain clinical controls and neglect of what is already known of the natural history of disease

In this chapter it is proposed to discuss the sites mechanism of invasion of the body methods of discovery of focal infection and the results of removal of infected foci from the body

Historical

The general recognition of the fact that symptoms of disease may be caused by some hidden and often symptomless lesion elsewhere in the body is a modern development, but there are numerous suggestions of this relation in older medical chronicles Benjamin Rush[1] advised the removal of a tooth for the cure of a patient afflicted with rheumatism and somewhat earlier Jean Louis Petit, surgeon of Paris 1674–1750 related his experience with dental infection and systemic disease Caries of a tooth is often the cause not only of (peria pical) abscess but of more extensive infections of the mouth and indeed of many diseases which appear to have but little relation to the teeth After enumerating the symptom including cough loss of appetite sleeplessness chills and fever from which one of his patients suffered Petit continues He was believed to have consumption and had been treated for this for a year I found that he had two carious teeth which I removed and within a few days all his symptoms disappeared

The records of the medical efforts of Arad Nana Assyrian physician priest of King Esarhaddon and of King Ashur bani apal (7th Century B C) take us back into antiquity[3, 4] In a letter to Esarhaddon who seems to have been suffering from an infection associated with fever Arad Nana advised the application of oils and licorice Later Arad Nana writes presumably to Ashur bani apal —

> ' — To the King
> To the King my lord your servant may it be well with the King my lord It is well with the overseer of the Divine Lady of Commands
>
> Regarding that which the King my lord has written According to your (usual) integrity send I have spoken the truth with the King my lord the burning of his head his hands (and) his feet wherewith he burns is because of his teeth His teeth should be drawn his residence should be sprinkled He has been brought low Now he will be well exceedingly

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The advice as well as the optimism of Arad Nana have an extremely modern and familiar sound Undoubtedly Ashurbanipal recovered, for he subsequently led an active life Ultimately he must have suffered from a recurrence possibly spondylitis as happens to so many patients of today, for in a later letter he complains 'Why has sickness woe of heart misery and destruction bound me? Destruction and an evil word are lined up against me ill of heart and ill of body have bowed down my form'

The Development of the Concept of Focal Infection

The advent of bacteriology and the correlation of pathologic changes, resulting from infections with the clinical course of disease facilitated the study of affections of the several organ systems Soon the possible relation of local disease such as that of the tonsils or teeth to other more general disease of the body was suggested W D Miller (1891) wrote on the human mouth as a focus of infection, and W Hunter[6] (1900) suggested oral sepsis as a cause of anemia and of 'neuritis and other septic conditions' Among still others were Curich (1904) and Schichhold[8] (1910), who discussed the relation of tonsillar infections to rheumatic disease and recommended the removal of infected tonsils for the cure of arthritis

In 1912 Frank Billings[9] reported the results attained by the removal of chronic local and often unsuspected infections from patients afflicted with arthritis neuritis and subacute and chronic parenchymatous nephritis He concluded his discussion as follows 'The purpose of this paper has been to call the attention of the profession to a source of general disease which while recognized by a few is entirely ignored by the many No one would say that the treatment advocated is specific in that all patients are made whole and well by it but it is believed that there is a principle involved as a cause of systemic disease which should be recognized should be sought for more frequently and when the focal infection wheresoever it may be located seems to be related to the systemic disease radical methods should be instituted to remove it When this is done those general measures which have long been recognized as essential to the well being of an individual should be instituted so that nothing will be left undone which may restore an invalid to health So far the experimental work done seems to prove clinically the truth of the principle *advocated*'

Through these and subsequent studies of Billings and his associates the importance of the concept of focal infection in the solution of many problems of formerly obscure disease came to be widely recognized, and the causal relation of hidden chronic local infection to certain recurrent lesions of joints nerves and other tissues was established

The formulation of the concept of focal infection was a logical development of the study of chronic disabling conditions many of which had not been shown to be related to infections but which at times presented symptoms resembling those of known infectious processes. Following the discovery of bacteria and methods of their culture the progress of clinical bacteriology had been amazingly rapid. Bacteriologic studies were, however, concerned chiefly with the relation of organisms to diseases already suspected on clinical grounds of having an infectious origin. The demonstration of bacteremia by blood cultures in streptococcal and staphylococcal sepsis, in typhoid fever and in lobar pneumonia suggested that other less severe infections might have a similar but relatively symptomless mechanism of distribution by the blood stream, a supposition which, if confirmed, would furnish an explanation of metastatic lesions which appeared possibly to be infectious. It was but a step further to the search for previously undisclosed sources of these metastases and when the quest for such hidden infections was rewarded by the finding of an unsuspected peritonsillar or other infection with relief to the symptoms of the patient by removal of the lesion, there was opened a new avenue of approach to a large group of disabling chronic diseases.

About the same time methods of roentgen photography were improved and unsuspected lesions of the accessory nasal sinuses and chest revealed. The dental roentgenogram disclosed a surprisingly large number of periapical dental lesions about supposedly sound teeth. Of more importance still, the necessity of painstaking and minute examination of the patient to determine the presence of abnormal and possibly infectious lesions was emphasized.

It was but natural that studies of chronic infections of this sort should center on chronic arthritis, the most important chronic disabling disease of temperate climates. The convergence of attention on this group resulted in the relief of a considerable number of patients with chronic recurrent infectious arthritis and stressed the importance of infection as one of the possible causes in still others, especially the atrophic type. It was the over emphasis of the concept of focal infection beyond the limits justified by facts which threatened for a time seriously to discredit a sound and important development in medicine. But even the excesses which grew out of the misapplication of the principles of focal infection contributed to a more thorough study of chronic arthritis with a resulting classification based on a clearer understanding of its complex and multiple etiology.

Studies of the effects of chronic local infections were extended to other diseases, among which were inflammation of the uveal tract of the eye, peripheral neuritis and certain of the myalgias. The desirability of freeing the body from discoverable chronic local infections before performing clean elective surgical operations was demonstrated, and the improvement in general health following

the discovery and removal of low grade chronic infections such as multiple alveolar abscesses was noted

Chronic Infection and Resistance

The sites of chronic infection in the body are many and include teeth, tonsils accessory nasal sinuses, prostate gland, gallbladder, to name only a few of the commoner Many people have one or more such infections for months or years without suffering from metastatic lesions in joints eyes, or elsewhere They may be entirely ignorant of the presence of infection in the body The chief factors that determine whether the infection shall remain confined to its local site, or whether it shall extend into adjacent or distant parts of the body may be grouped under three headings (1) the virulence or invasiveness of the organism ( ) the kind and extent of the infected tissue, and (3) the resistance of the host

Bacteria vary widely in their ability to invade and produce changes in animal tissues This variableness of action depends on a number of conditions, among which are the state of the micro organism the presence or absence of available food supply suitable oxygen tension and the degree of protection afforded the bacteria against the fluids and cells of the host One animal species may be naturally resistant or immune to infection by a particular organism whereas another species may be susceptible Also individuals of the same species may differ widely in their susceptibility to a given infection This difference in individuals frequently is observable in man

We commonly think of a virulent organism as one which like the streptococcus in erysipelas or cellulitis is able rapidly to invade the tissues with resulting edema pain and stormy illness This conception while correct so far as it goes, is incomplete and should not divert attention from those infections which proceed more slowly often unnoticed for a time but in which the invasion of the host by the bacterium is no less serious in its results Infection of the latter type is illustrated by some of the common forms of tuberculosis and syphilis Metastatic diseases of joints and eyes arising from infections about the teeth and other localized areas throughout the body resemble in their chronicity and in the relative absence of symptoms of systemic disease chronic rather than acute infections although all degrees of acuteness of both primary and secondary lesions may be encountered But even in chronic infections the process of invasion consists of a series of short steps rather than of one continuous process

Changes in cultural characteristics including the phenomena described under dissociation and in ability to invade the animal body have been observed in bacteria following their growth in the culture tube and it has been assumed

that changes in invasive power occur during their residence in a localized area in the body It is possible that such modifications occur, but conclusive evidence of these changes is difficult to obtain, and instances of variations in the disease producing power of organisms become relatively insignificant, when compared with the striking uniformity of growth and pathogenic qualities of most disease producing bacteria Epidemics of contagious disease vary in severity and in mortality from season to season and even during the course of a single epidemic but the cultural characteristics of the organism and the clinical features of the disease in the typical case are remarkedly constant Typhoid fever lobar pneumonia and epidemic meningitis present the same clinical pictures today as they did years ago, and the bacteria that cause them show the same general cultural characteristics

The term elective localization has been applied to the phenomena of invasion of special organs or tissues by bacteria assumed to possess or to have acquired peculiar qualities which enable them to survive and produce lesions in one organ or tissue rather than in another The observations adduced in support of this theory may be explained perhaps better by considerations of vascularity oxygen tension and hydrogen ion concentration of tissues and suitability of food supply relative to the special requirements of the invading bacteria

It thus appears that in our inquiry into the mechanism of metastatic infectious disease we must look also to the site and extent of the infection and the resistance of the host

The Extent and Behavior of Chronic Infections

One of the outstanding and puzzling factors encountered at the outset of a survey of chronic localized infections is that while many patients present themselves with evidence of metastatic lesions that evidently have their source in a chronically infected area of tissue there is a much larger number of persons who are subjects of chronic local infections of equal or even greater extent caused by the same kinds of bacteria who show no evidence of secondary infection in the joints or organs of the body At first glance such chronic infections might seem to differ in this respect from the acute infections arising from minor wounds but a moment's consideration will show that for one pin prick abrasion or cut that is followed by serious local or general infection there are tens or scores of similar wounds incurred under conditions that render likely the introduction of pathogenic bacteria into the wound which promptly heal without symptoms of infection

The reactions of the cells and fluids of the body against impending bacterial invasion which we are accustomed to speak of as resistance determine

to a large extent the outcome of a local infection, no matter whether it is acute or chronic This resistance to invasion, however, is not a constant quantity, but rises and falls in consequence of changes in nutrition, or because of fatigue exposure to cold or other favorable or unfavorable influences of environment The course of an acute infection thus is determined by the virulence of the organism the extent of the area of implantation and the resistance of the body at the time of the infection In chronic local infection the infecting bacteria are afforded a safe residence in which they may multiply, and from which they may invade the body intermittently, when its resistance is lowered temporarily

The tissues involved in the local chronic infection may be in close connection with normal tissue, or they may be surrounded by a fairly firm wall of granulation and connective tissue which affords some degree of protection to the adjacent uninfected structures There is, however, a fairly direct communication between the local lesion and surrounding tissue by means of lymphatics and blood vessels Even in so isolated a lesion as an alveolar abscess, lymph channels pass out to surrounding bone and subjacent tissues, and as Noyes[11] has shown the lymphatics below the jaw can be injected through the pulp chambers of the teeth of the mandible The enlarged regional lymph nodes found in association with chronic infections of the mouth and tonsils indicate the close lymphatic connection between infected areas and surrounding tissues

The degree of confinement of the infected area influences the passage of organisms through lymphatics and blood vessels and metastatic infections result more often from lesions entirely closed either acute or chronic, than from those in which external drainage is free Trauma of an infected lesion, such as the squeezing of a furuncle, favors the spread of infection to surrounding and distant tissues Injury of previously healthy tissue may reduce local resistance sufficiently to allow the survival and multiplication of organisms brought thither from an infected region

The defenses of the body against bacteria which have passed the skin or mucous membranes, or have entered through the gateway of chronic localized infections, are maintained by means of the antibacterial action of the fluids of the body, by the leukocytes and other phagocytic cells or by combinations of these Several of these reactions can be demonstrated in the test tube and have received various descriptive names such as phagocytosis While some estimate of the probable resistance of the body to impending infection can be made by means of these reactions in the laboratory it is possible that the mechanism of bodily defense involves other or more intricate chemical reactions which thus far have eluded demonstration by the means at our command

In view of these many circumstances, one of which or several in combination

may serve to favor or to prevent the passage of organisms from a chronically infected area to other places in the body, it is not surprising that such infections may produce metastatic lesions in one person and remain symptomless in another or that an infection which has remained quiescent and unrecognized for years suddenly may cause widespread and disabling disease

Immunity or resistance to infection is only relative and the fine balance may be turned unfavorably to the patient by divers agents just enumerated Immunity, which is sufficient to protect against the degree of exposure ordinarily encountered may prove ineffective when the dose of infecting organisms is increased Antityphoid inoculations confer an increased immunity to typhoid fever and persons so inoculated do not contract typhoid even when they occasionally ingest typhoid bacilli in numbers usually met with in polluted water If, however, the same persons are exposed by the ingestion of heavily polluted water as happened to certain companies of soldiers in France in the World War they do contract typhoid fever The danger of presuming too much on natural immunity is seen in the serious infections with sometimes general sepsis and death which occasionally follow the extraction of many infected teeth at one time The dental axiom that, when many infected teeth are to be removed only two or three should be extracted at each sitting at intervals of several days expresses in terms of dental practice the necessity of conserving the resistance of the patient by avoiding an overdose of infection through increasing the area of fresh wounds of tissue and lymphatic vessels

The Mechanism of Invasion

Metastatic invasion of joints or bone in streptococcal pneumococcal or staphylococcal infection associated with bacteremia is easily accounted for by the transport of organisms in the blood stream Likewise in gonococcal infections the occasionally demonstrable gonococcemia and the isolation of the gonococcus from joint fluid in some cases show the means by which the organisms pass from the site of infection in the urethra and prostate to distant parts of the body A similar mechanism must be considered in the more chronic and clinically less evident infections in tonsils or alveolar abscesses which seem to bear a similar causal relation to recurrent and chronic arthritis The study of transient and symptomless bacteremia by blood cultures has been pursued with great diligence by some students of chronic arthritis in the search for facts which might be of help in classification of arthritis and in the finding of immunologic reactions significant in determining etiology and therapy Studies of blood cultures in chronic arthritis have resulted in the finding of streptococci and other organisms in chronic arthritis in widely varying proportions by different workers Some differences undoubtedly

are due to the use of more favorable culture media and also possibly to the types of cases included in the several series In general, larger numbers of positive blood cultures have been reported in atrophic arthritis (arthritis deformans) than in osteoarthritis Other evidences of infection, slight fever, rapid pulse and involvement of soft tissues and cartilage more frequently noted in atrophic arthritis in younger persons as contrasted with bony proliferation, absence of evidence of infection frequently with vascular changes and arteriosclerosis, seen in osteoarthritis in older persons would lead to the expectation of a larger element of infection in the atrophic than in the osteoarthritic type of arthritis

There is however some question as to the real significance of the demonstration of occasional organisms in the blood Rieth and Squier[1] made cultures of the blood of a large number of supposedly normal workers who were given a complete routine examination in a large manufacturing plant These persons were examined carefully for evidence of non disabling disease and for chronic infection which had not as yet caused symptoms sufficient to lead them to seek medical advice In 27 per cent of 194 persons who had chronic local infection and in 12 per cent of 99 persons without demonstrable local infection they obtained in blood cultures occasional organisms which could hardly be regarded as contaminations These results suggest that even in persons in good health organisms may enter the blood stream and be recovered from it by cultural methods before they have been destroyed by the cellular and humoral protecting mechanisms of the body

While the significance of occasional organisms in the blood must be appraised with some caution it seems clear that one definite mechanism of production of symptoms in distant organs and tissues is by transport by the blood of organisms which enter through or reside in a local focus in the body On the other hand some of the organisms recovered in blood cultures may be accidental invaders, and therefore not necessarily related to the disease under investigation

Allergy

A second and perhaps less well recognized and understood mechanism of production of symptoms in joints eyes skin and other tissues is concerned with the condition known as allergy Urticarial and hemorrhagic lesions often follow repeated injections of foreign serum and may be accompanied by non infectious arthritis characterized by joint pains and swelling The production of allergic responses, either local in the skin or general by the products of bacterial growth such as tuberculin and other bacterial filtrates is used in diagnosis and to a limited extent in treatment At present increasing attention is being given to the possible allergic nature of certain of the symptoms of infectious disease such as the re

current and shifting joint swellings and cutaneous lesions in acute rheumatic fever Similarly some of the recurrent swelling and pain in joints in chronic arthritis, notably those exacerbations which sometimes follow minor colds and inflammation of the pharynx may be due to allergic respon e rather than actual bacterial reinvasion

Studies of human arthritis and that produced in animals are responsible for many of the conclusions regarding the relation of local infection to metastatic disease but these studies are complicated by other factors such as the trauma of motion and by the inacce ibility of the interior of joints to visual observation of successive tissue changes Acute recurrent iritis and recurrent arthritis are some times observable in one patient and the mechani ms of recurrences in joints and eyes presumably are the same A restatement of the apparent mechanism of metastatic infection as it occurs in the eye in which alterations in tissues can be readily seen may throw light on some of the processes which determine the cour e of arthritis and other lesions associated with local infection

Mechanism of Production of Iritis

The original invasion of the eye may be and in certain infections in man and in animals it has been shown to be due to actual bacterial lodgment and organ isms have been recovered from the lesions Subsequent recurrences in the arrested lesions in the eye may be due to recurrent bacterial lodgment although the theory of probabilities may be urged against this

In acute endogenous non recurrent iritis the conception of fortuitous em bolic bacterial lodgment seems to offer one reasonable explanation of the pro duction of the lesion by organisms resident elsewhere in the body and tran ported by the blood stream in the course of a bacteremia This bacteremia may be demonstrable by culture as in streptococcal sepsis or in meningococcal infections to employ examples of diseases in which the invading organism has been found in the ocular lesion or may be almost symptomless as in other cases of acute iritis which also seem clearly to be due to local infection The apparent natural resist ance of tissues of the eye suggested by the absence of symptoms of ocular lesion in many and indeed the majority of cases of known sepsis and other bacteremias is not peculiar to the eye but is also shared by other tissues of the body in which frequently there is no evidence of metastatic disease In diseases such as lobar pneumonia typhoid fever sep is or osteomyelitis originating in a furuncle in which there is a tran port of organisms by the blood stream the development of a lesion in joint bone or eye is less extraordinary than is the paucity of metastatic lesions

In consideration of the few symptom producing metastases observed in diseases

with known bacteremia the relative rarity of iritis resulting from frequent chronic local lesions with minimal and usually undemonstrable bacteremia occasions no surprise

Sensitization of Ocular Tissues

Recurrences of iritis in the same eye, and the exacerbations of chronic iritis raise questions which seem to require for their answers something more than bacterial embolism While it is probable that tissues of the eye previously injured are more susceptible to bacterial reinvasion, it is also possible that the exacerbations of ocular irritation may be due to bacterial toxins generated in the original or other focus which excite a reaction in the uveal tract already specifically sensitized by the first attack

A I Brown[13] has shown experimentally in rabbits that recurrences of inflammation of the uveal tract can be produced by the intravenous injection of bacteria, egg white foreign erythrocytes or streptococcal toxin, in eyes previously injected intraocularly with the corresponding antigen

The removal of a focus of infection, such as a tonsillar abscess thus may be effective in preventing recurrence of iritis whether the actual exciting cause originating in the tonsil and acting on the sensitized eye be the bacterial body or a toxic protein derived from its growth

Now and then the removal of the tonsils or the extraction of an infected tooth is followed within a few hours by the sudden subsidence of symptoms and disappearance of inflammation in an eye in which acute inflammation of the uveal tract was present The same amelioration of symptoms occasionally follows the injection of foreign protein When tuberculin is given subcutaneously in sufficient dosage a focal reaction may occur in the affected eye with increase in symptoms and signs of inflammation These familiar observations suggest that allergy of the involved ocular tissues is an important factor in the clinical course of iritis

Cases of chronic and recurrent iritis have been observed in which after the exclusion as completely as clinical and laboratory tests allowed of tuberculosis and syphilis, and after the removal of all recognizable other causes, recurrences of the iritis continued following minor attacks of pharyngitis, or acute colds Certain of these patients are extremely sensitive to some streptococcal filtrates and not to others Just how specific this sensitivity will prove to be is undetermined, but such observations may be helpful in the study of certain cases of chronic and recurrent iritis and indicate that allergic phenomena as well as embolic, arising through bacteremia are concerned in the production of symptoms

It thus appears that in the mechanism of production of the structural lesions and symptoms in arthritis and in iritis there are to be considered both bacterial

invasion of the blood, often slight and symptomless and an allergic state produced by previous infection of the affected tissues

If both these factors are recognized the presence or absence of bacteria in the blood during recurrences of the local lesion becomes less a prerequisite for the acceptance of the causative relation of local infection to distant metastases, and more significant of the general state of resistance of the patient

The Sites of Focal Infection

The more commonly identified sites of infection are the tonsillar regions the roots of teeth the accessory nasal sinuses and the prostate gland Chronic infections in these regions may have been preceded by known acute infections such as acute tonsillitis or sinusitis or in perhaps a larger number of patients there was no acute infection noted or its occurrence had been forgotten

Tonsillar Infections

In chronic infection in the tonsillar regions there may be a history of recurrent tonsillitis or of peritonsillar abscess The presence of enlarged regional lymph nodes a dusky redness of the anterior pillars and evident scarring of the tissues about the tonsils are suggestive of chronic infection Fluid pus sometimes may be expressed Simple enlargement of the tonsils or the expression from the crypts of yellowish concretions consisting of food remnants and epithelial cell are not evidence of chronic infection The removal of greatly enlarged tonsils and hypertrophied pharyngeal lymphoid tissue may be necessary for mechanical reasons but this problem should not be confused with that of focal infection The chronically infected tonsil is often small fibrous from repeated infections and concealed within or behind it there may be a small abscess

Dental Infections

The most important means of discovering periapical infections of the teeth is the roentgenogram With the introduction of the roentgen film many supposedly sound teeth usually those with extensive fillings or functionally restored with crowns were found to have areas of absorption of the alveolar bone surrounding their apices On removal of such teeth the periapical spaces were found to contain granulation tissue and leucocytes and frequently bacteria were grown from them Adequate dental treatment or removal of teeth with periapical abscesses has not infrequently been followed by recovery from recurrent arthritis and iritis Metastatic infection from pyorrhoea is less clearly demonstrated but in some patients the

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It thus appears that in the mechanism of production of the structural lesions and symptoms in arthritis and in iritis there are to be considered both bacterial

Infections of the Accessory Nasal Sinuses

Chronic infections of the accessory nasal sinuses may follow known acute infections or may develop without previous recognized symptoms Improved roentgenologic technique and more searching methods of clinical examination have led to the discovery of sinus infections previously missed but as with infections of the teeth their presence does not always result in metastatic lesions and their treatment may or may not be followed by recovery from the condition such as arthritis for which relief is sought There is frequently no nasal discharge and headache may be slight or absent Abnormal shadows on the roentgen film may be due to anatomic deviations from the normal in bony structure or in size of the sinuses or to thickening of the lining of sinuses resulting from old but healed infection The diagnosis of active sinus infection should be based on physical examination as well as on the radiograph The maxillary and ethmoid sinuses seem to be involved most frequently and the frontal and sphenoid less often

Infection of the Prostate Gland

Chronic prostatic infections may follow months or years after acute infections or they may occur in persons who have never previously had any known infection of the genito-urinary tract Prostatitis often follows gonococcal urethral infections and may persist for months after acute symptoms have subsided or even for years after the gonococci are no longer demonstrable In the earlier and more acute stages periprostatic phlebitis may occur and bacteremia and multiple metastases in joints result In other adults who never had gonococcal infection prostatic infection may follow acute respiratory infections or tonsillitis and persist for months as a chronic infection which is likely to be missed unless routine examination of the prostate is made

Examination of the prostate per rectum will determine the size consistence and degree of tenderness and examination of the expressed secretion and of the urine before and after massage may show pus cells and bacteria Chronic prostatic infections frequently are associated with chronic arthritis and with acute or recurrent iritis Some of these are gonococcal but others are clearly of non venereal origin

Other Sites of Chronic Infection

Less commonly encountered sites of chronic local infection are the gall bladder lymph nodes about the hila of the lungs perirectal abscesses ulcerative

favorable effect on the general health of the removal of teeth extensively affected with pyorrhoea i unquestioned

In contrast with the undoubted good results, which have followed the detection and removal of alveolar abscesses must be placed the ill effects on the general health and peace of mind of patients of the needless removal of teeth in the hope that improvement of arthritis perhaps due to some other cause, might result The wholesale and ill considered removal of sound teeth constitutes one of the chief counts in the indictment against the excesses committed by some early enthusiasts for the theory of focal infection

The ruthless sacrifice of sound teeth has ceased largely, but there still remains the problem of the "dead tooth which has divided dentists as well as physicians into two camps When the pulp of a tooth dies, the tooth becomes insensitive to electrical or caloric stimulation but the peridental membrane between the tooth and the surrounding alveolar bone may still be intact, and the tooth sound and serviceable An apical alveolar abscess is incompatible with a live pulp, and hence teeth with periapical infections are insensitive but the converse proposition that insensitive teeth are infected and therefore, should be removed does not hold Absence of sensation in a tooth requires increased vigilance and re examination by the qualified dentist, but does not alone call for its removal Questions as to the interpretation of roentgen films frequently arise and are to be decided after consultation with a qualified dentist and a consideration of other circumstances of the patient s illness In a patient, who suffers from a serious iritis of his only remaining eye the treatment of a tooth the radiograph of which indicates possible periapical ab orption is likely to be more radical than if the patient were the subject of arthritis of doubtful infectious origin

Periapical absorption with possible infection is extremely frequent and increases in incidence with each decade of life but does not necessarily give rise to metastatic lesions In radiographs of the teeth of 124 patients in Cook County Hospital, some years ago, we found evidence of aveolar abscesses in 44 per cent When these patients were classified as to the diseases from which they suffered, alveolar ab cesses were found in 76 per cent of the arthritic group, in 47 per cent of the cardiovascular group and in 23 per cent of the remainder which included acute diseases such as typhoid fever and pneumonia Studies by others have shown still higher percentages Arthur D Black[14] in a radiographic study of 600 adult dental patients found 78 per cent showing areas of bone destruction In 72 per cent there were as yet no evidences of systemic disease The interpretation of the significance of dental infection when it is found coexistent with arthritis obviously requires caution The dental lesions may be related etiologically or they may be coincidental Finally the dental disease itself may be secondary to local infection elsewhere

of joints of the hands often ulnar deflection and later ankylosis The onset is insidious or acute In many patients constitutional effects with slight fever anemia and poor nutrition are evident

Hypertrophic arthritis (osteoarthritis) is found in persons at or beyond middle life often well nourished and produces disability varying from slight to severe crippling Usually it is polyarticular but may be monarticular Lipping of joints and hyperostoses are frequent ankylosis is rare Fibrous thickenings Heberden s nodes with later bony hyperplasia at the terminal joint of the fingers are frequent The effects of the trauma of work are often noted in the hands and spine of the laborer

Evidences of active infection both clinical and laboratory, are more frequent in the atrophic than in the hypertrophic group In some patients with atrophic arthritis removal of local infection is clearly beneficial and may contribute to recovery but in others there is little observable effect and the illness is to be combatted rather by measures directed to improvement of general and local nutrition

In chronic arthritis characterized by changes of the hypertrophic group infection seems to play but little part in the progress of the disease There are of course exceptions and even the sites of Heberden s nodes frequently seen in this type of arthritis may show evidence of acute inflammation with redness swelling and tenderness following acute infections elsewhere in the body Local infections especially in the mouth frequently are found but their removal while desirable on general grounds does not usually affect the course of the disease

Each patient with chronic arthritis presents an individual problem His illness is to be regarded as a general disease one of the outstanding features of which is the disability of one or many joints Chronic local infection is one of the possible causes and should be searched for and corrected if found The therapeutic result will depend on the relative causative importance of the infection It must also be remembered that spontaneous remissions occur in chronic arthritis and this fact together with the favorable effects of rest and other measures taken in the care of the patient are to be considered in assessing the apparent benefit from the removal of the infection

Iritis

Acute and recurrent endogenous iritis or uveitis offers an interesting field for the study of the incidence of chronic infections and of the results of their removal in a group of persons in whom the progress of the local disease of the eye can be followed relatively unaffected by trauma of motion and use unavoid

lesions of the colon and other local lesions in which there is persisting low grade infection from which invasion of the body may take place during exacerbations of the infection or by reason of lowered resistance of the body Any lesion or break in the integument or mucous membrane may, conceivably, serve as the portal of entry of organisms which set up general or local infections of the body but such an inclusive conception is not involved in the commonly accepted definition of focal infection

Clinical Applications

Chronic local circumscribed infections are manifestly of frequent occurrence in man and their incidence increases with advancing years Sometimes they are residual infections in tissues previou ly the site of disease at other times they develop without any preceding symptoms They may produce local changes which lead directly to their detection, or they may be symptomless and remain unnoted until special search reveals their presence It is the large number of local infections in apparently healthy persons which seem not to interfere with the general health which has led some to question the validity of the conclusion that the removal of local infection results in the cure of alleged metastatic disease such as that in joints or eyes The difficulties of estimating the significance of any one infection as a cause of disease are greatly increased when multiple local infections in several ti sues teeth, tonsils, prostate, are encountered

Recurrent and Chronic Arthritis

Much of the discussion as to the significance of focal infection in medicine has centered about its relation to arthritis In general chronic arthritis is to be thought of as a systemic disease of which the changes in the joints are one manifestation[1]

The division of chronic arthritis into two groups (1) chronic atrophic (rheumatoid) arthritis and ( ) chronic hypertrophic arthritis (osteoarthritis) facilitates clinical study with respect to morbid anatomy and especially to the relative importance of infection in the two groups Such a classification is useful in planning treatment and in prognosis whether one holds that the two groups represent separate disease entities or whether one regards chronic arthritis, as does the writer as the resultant of one or more of many possible causes whose course is determined by the age of the patient the quality type of reaction and nutrition of his tissues and their exposure to further trauma

The characteristics of atrophic arthritis are its incidence chiefly in younger persons, especially women multiple joint involvement with fusiform appearance

tuberculous infection is certainly lower in acute iritis and higher in the extremely chronic recurrent cases The incidence also of chronic local infections is higher in dispensary and general hospital than in private practice

Other Conditions Ascribed to Focal Infection

The same general principles followed in the study of arthritis and iritis are applicable to the search for the underlying cause of other manifestations of the distant effects of chronic local infections Conditions such as certain myalgias and painful nerves and the more general constitutional results of toxemia expressed for example by anemia or by interference with the physiologic functions of the kidneys seem to be due sometimes to the toxic or systemic consequences of local infection

It is important therefore to examine patients carefully with such possibilities in mind, but at the same time to remember that pains and anemia may be due to unsuspected metastases of malignant tumors to mechanical pressure on nerves or to the effects of unrecognized general infectious disease Enthusiasm should be tempered by clinical judgment

Whether studied in relation to a single di ea e or in a search for the cause of other perhaps poorly defined clinical pictures the problem of focal infection is to be regarded as only a limited part of the larger problem of susceptibility and resistance to infection Chronic circumscribed infections may contribute to the illness of the patient or may exist fortuitously in persons suffering from infections of other sorts or from non infectious di eases The removal of chronic infections whose etiologic relation to the patient s disability is not clearly demonstrated may of course benefit the patient indirectly by removing a load which interferes with his recovery The results of search for local infection must therefore, be utilized after a consideration of all the facts ascertainable in each patient

The contribution of the concept of focal infection to medicine consists in the recognition of the importance of chronic local and often symptomless infections as possible causes of disease in distant parts of the body and in the accentuation of the necessity of careful painstaking examination of each patient

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able in joints In a study of 100 cases of iritis[16], in which careful search was made for chronic local infections as well as for evidence of syphilis and tuberculosis it was noted that while in some cases one infection alone was discovered there were many instances in which multiple sites of infection were found

The findings recorded in Table 1 illustrate what may be found in a study of approximately equal numbers of patients in dispensary and in private practice

TABLE I

INFECTIONS FOUND IN TWO HUNDRED CASES OF IRITIS

Infections	*None*	*With Other Infections*	*Total*	*Coincident Infections*							
				Syphilis	*Gonococcal*	*Tuberculosis*	*Dental*	*Tonsillar*	*Sinus*	*Non-venereal Genito-urinary*	*Other Infections*
Syphilis	12	26	38		8	6	13	10	3		
Gonococcal Infection	8	2	10				1	1			
Tuberculosis	8		8								
Dental Infection	12	[illegible]	27		2	2		9	3		
Tonsillar Infection	6	[illegible]	53	5	3	4	22		1	1	1
Sinus Infection	1	3	4				2	1			
Genito-urinary nonvenereal	6		6								
Other infections	3		3				1				
No infection found			3								
Combined infections		41	41	15	1	11	7	35	15	1	5
Undetermined		[illegible]	7	3		1	2	1			2
Total			200								

The incidence of any one kind of infection will be influenced by the group incidence of diseases such as syphilis or tuberculosis, and by the economic status and intelligence of the population from which the patients come

In a large proportion of patients with acute iritis removal of localized infections was followed by recovery from iritis and freedom from recurrences during periods of observation of from two to twelve years In the more chronic recurrent forms of iritis the removal of chronic detectable local infections often failed to prevent recurrences an observation which taken with other observed facts, suggests that in such patients additional factors such as allergy, already referred to are concerned There also seems to be no question that chronic recurrent uveitis frequently is attributable to tuberculous infection But a clinically similar course is observed in persons in whom there is no demonstrable evidence of tuberculosis and in whom recurrences of iritis occur following minor infections such as pharyngitis and acute colds In general the incidence of detectable

CHAPTER IV

THE MECHANISM OF RESISTANCE TO DISEASE

By FREDERICK P. GAY

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Sept 1 1935

The three main bodies of facts then Symptomatology Morbid Anatomy and Etiology form the basis on which disease entities have been determined and on which diagnosis in the individual case depends

A more inclusive arrangement of disease entities than is required by the diagnostician is necessary for those who would construct a System of Medicine , a Textbook of Pathology or who would attempt to collect morbidity or mortality statistics The science of the classification of diseases Nosology is an ancient one so ancient indeed and so metaphysical in its beginnings that it has fallen into the disfavor of a more scientific age Nosology has followed chronologically the successive development of the bodies of facts on which it is founded It has been based successively on Symptomatology on Anatomy and on Etiology In its earliest phases when objective facts were few and speculation unrestrained systems of nosology were completely explanatory and individual The taxonomic systems of Sauvages and Linnaeus (1763) of Cullen (1764) and of Good (1823) were rationally complete but each was different and all were in disagreement with present day information Anatomical correlation in these earlier attempts at classification was incidental and often inaccurate

The great development of Morbid Anatomy in the nineteenth century beginning with the work of Morgagni (178) led to exact information of the changes in organs tissues and cells as a result of disease and gave a new and more accurate basis of classification Although in many respects less complete than Symptomatology Morbid Anatomy has formed a surer foundation on which to establish essential disease characteristics Many diseases however present no definitely recognized structural changes or are accompanied by lesions which are common to several disease processes Morbid Anatomy is misleading in that it over-emphasizes structural changes rather than the functional changes which must precede them and draws attention to the end rather than to the beginning of disease processes

The development of the sciences of Bacteriology Protozoology and Parasitology has proved beyond question that certain diseases are produced by extrinsic living agents In addition their establishment has rendered possible the grouping of certain diseases long known as fevers and later classified as infections on the basis of specific causation A Nosology based on etiology is not only logical but has become increasingly complete in the few years since the science of Bacteriology became formulated (about 1880) Recent treatises of medicine and particularly of pathological anatomy (Krehl and Marchand MacCallum) have begun to group their facts so far as they are available in accordance with causal agents There remain however many diseases of which we do not know the cause which fact has forced systematists to adopt a heterogeneous basis of classification on the basis of etiology of anatomical change and of symptomatology

Introduction

No intelligent conception of resistance to disease can be formulated without consideration of the nature and causation of disease processes in general and particular. This preliminary consideration is essential since each separate instance of disease in susceptibility, resistance, tolerance, or immunity involves a mechanism which is specific, that is to say, operative solely against a particular causative agent.

The nature and causation of disease has interested reasoning mankind in a very personal way since the beginning of human history. There is no need at this point to consider the purely speculative considerations of the relation of disease to supernatural agencies, the association of medicine with religion, the concurrence of epidemics and planetary commotions, nor yet the purely metaphysical concepts of humoral changes and balances conceived by the earliest physicians. The more concrete correlations of seasonal variations, disturbances in the soil and the like are still recognized as adjuvant factors in disease causation. Certain useful conceptions and practices, such as the idea of contact infections and quarantine, may be traced to these earlier ideas.

Medicine in common with other sciences has developed through increasingly perfected methods of observation. The ancient physicians contributed one of the permanent objective technics to modern medicine, the observation of symptoms in the patient. The present day understanding of the nature and causation of disease may be attributed particularly to the building up of two additional groups of facts, namely, the detection and appreciation of changes in diseased bodies and tissues (Morbid Anatomy and Histopathology) and demonstration of the existence of external animate agents of diseases (Bacteriology and Protozoology). In addition, a newly appreciated mode of approach, the experimental method, has accelerated enormously the accumulation and ordering of the facts grouped under Symptomatology, Pathology and Etiology.

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This classification on the basis of etiology is to repeat designed simply to facilitate discussion of the defense mechanisms of the body which are in their essence specific It is safe to venture the assertion that the group of 'unknown diseases will steadily decrease numerically It is less certain but likely that all diseases including these now designated as endogenous will be traced eventually to an external source

The relative vital importance of the different etiological groups of disease cannot of course, be estimated on the basis of such an academic grouping as the total number of disease entities It may be of interest to estimate that approximately one half of all the diseases we now recognize are due to living micro-organisms but it would be of far greater importance to learn what percentage of the actual instances of disease are due to these agents Reliable morbidity statistics on which to base such conclusions are not available particularly if we consider minor ailments like the common cold that seldom come to the attention of the physician We have only the reportable diseases which are all infectious in nature and mortality statistics on which to base an estimate of the real importance of each group

With this excursion into the field of disease causation and of nosology, we may now approach a systematic consideration of the defense mechanism of the body against disease in general

1 Defense Mechanisms in Diseases of Unknown Causation

The recognition of given bacteria as the active agent in producing a series of infectious diseases has facilitated enormously recognition of defense mechanisms that exist in the animal body against them and has given us means of increasing artificially these protective agencies It is of course true that conditions of natural and acquired immunity were appreciated long before Bacteriology existed as a science and smallpox vaccination has been practiced for over a century whereas its inciting agent still eludes us But at all events from analogy we should expect difficulties in appreciating defense reactions that may exist against unknown causes of disease Most of the diseases of this unknown category differ from the acute infections in such a way as to make discovery of a protective mechanism more difficult they are more insidious in onset and not readily suspected in their initial phases where resistance would probably be more evident And again these diseases do not tend to spontaneous recovery which might be followed by a condition resembling acquired immunity

The adiposity which so frequently precedes diabetes mellitus (Joslin) may represent when deficiency in the sugar splitting mechanism begins to be felt a more or less successful attempt to store carbohydrates that otherwise would be wasted The glycogen stores are filled first and then fat deposition occurs both

It occurred to us some years ago that a classification of diseases on the single basis of etiology was not only logical and desirable but could actually be made temporarily complete by erecting a group designated "Causation Unknown" It interested us further to catalogue the recognized disease entities on an etiological basis and to obtain some estimate of the relative numbers in each division The recognized disease entities in one of the larger systems of medicine (Osler and McCrae) and in certain specialized treatises on diseases of the eye and of the skin were listed carefully in groups on the basis of accepted etiology Whenever there was a well maintained dispute as to whether the causative agent is animate inanimate or essentially unknown, it was listed under each of the groups in question This list was later checked by a similar grouping from the nomenclature list of diseases and injuries in the manual of the Medical Department of the United States Army

Three well defined groups of disease agents emerged, animate, inanimate and unknown The animate and inanimate agents were found to be operative in fifty and thirty per cent respectively of the total number of separate disease entities listed These animate and inanimate agents are known to be extrinsic, whereas certain of the diseases of unknown etiology are assumed to be endogenous These are the so-called metabolic constitutional, or nutritive diseases Table I presents in graphic form the attempt to create a potential Nosology on the basis of Etiology

TABLE I A POTENTIAL CLASSIFICATION OF DISEASES ON THE BASIS OF ETIOLOGY

Causative Agent	Per cent	Type of disease produced	Type of resistance evidenced by host
Animate	50		
Bacteria Yeast and Moulds Spirochetes Rickettsia Viruses Protozoa Parasites		Infections	Natural Resistance Immunity
Inanimate	30		
Physical Chemical Poisons Protein Deficiencies		Injuries Intoxications addictions Hypersusceptibility Avitaminoses	Tolerance Habituation
Unknown	20	Metabolic Constitutional Endocrine (Endogenous or Idiopathic)	Unknown

The traumatic or mechanical causes of disease produce wounds of various sorts and pressure disturbances The analysis and treatment of the resultant lesions is the affair of the surgeon but we are concerned for the moment with a description of the mechanisms that exist in the body for preventing and re pairing them The relatively impervious skin offers a resistance to the inflic tions of wounds that is not present in the softer and more vital tissues The presence of nerve terminals and the consequent sensation of pain in exposed parts accomplish the definite purpose of giving rise to muscular action that tends to avoid further injury These reflexes, as is known become distinctly more active as a result of physical training The mechanism set in action by rage or fear which Cannon has described so romantically and yet scientifically, obviously is designed to protect the body against mechanical injury A blow actual or anticipated or even the catching sight by a cat of its hereditary enemy, the dog sets in action a most complicated protective reaction An increase in the activity of the adrenal glands occurs and this in turn calls forth stored carbohydrates from the liver into the blood The blood by periph eral vasoconstriction is sent directly to the muscles thus supplying them with sugar and rendering their action in fight or flight more effective Adrena lin moreover diminishes fatigue in muscles and increases the rapidity of blood coagulation so that in cases of wounds there is less danger from bleeding Pain itself once an injury has taken place is to some extent diminished by the muscular effort of writhing (Dumas)

Foreign bodies whether simply lying on the surface of the body or lodged in the respiratory and alimentary tracts are potential traumatic agents either in themselves or as leading to secondary infections The reflexes of sneezing coughing and vomiting are the first protective mechanisms designed to get rid of these foreign particles When foreign bodies have penetrated beneath the superficial layers of the body the phenomena of inflammations are designed to segregate include or expel these extraneous agents

Repeated minor injuries to the surface of the body if not too severe lead to a thickening of the epidermis or callosity and destructive injury leads to a process of repair characterized by the overgrowth of connective tissue (cicatrix) which is denser than epithelium and therein better able to protect against future injury

Any considerable change in atmospheric pressure gives rise in animals not only to symptoms but, in man at least may produce well defined disease Among these diseases are mountain sickness produced by altitude and dimin ished oxygen pressure caisson disease produced by too rapid a change from increased to normal atmospheric pressure and seasickness which is due at least in part to variations in pressure in the semicircular canals of the ear There is not so far as we are aware evidence of habituation or increased resistance to

of which eventually are called on when glucose can no longer be ut ed The fact that the blood sugar concentration is higher in the diabetic tha normal is further evidence of an adaptive mechanism to prevent waste

Another instance of a distinctly different sort and resembling th enon ena of bacterial immunity, has been found in the experimental studies he m lig nant tumors of rats and mice Different races of mice vary in th susc pti bility to any given transmissible tumor A second tumor fails to when a flourishing one precedes it (Ehrlich s athreptic immunity) The wth of a tumor in otherwise susceptible animals may be prevented by pre moc ili tions of normal mouse tissue, particularly embryonic tissue G g tun rs in rats may be caused to retrograde by injections of tumor tissue (ay)

These two instances have been offered simply to indicate that de ise mech nisms may be present in diseases of which we have as yet failed recogr ze the causative agents The appreciation of further instances of th is sort a l methods of enhancing such natural protective mechanisms will d btless w it on further discovery in the etiology of these obscure maladies

II Defense Mechanisms in Diseases due to Inanimate Exogenous Agent

Reference to the table that outlines a pc the basis of etiology will show that the e into two large groups respectively of physi are natural individual variations in the re of these groups The mechanisms resp may occur have been investigated in the fact that these defense mechanisms the degree of resistance thereby nature the increase of resistance is ation acclimatization training ar designation, tolerance or habit at

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Tolera

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These two instances have been offered simply to indicate that defense mechanisms may be present in diseases of which we have as yet failed to recognize the causative agents The appreciation of further instances of this sort and methods of enhancing such natural protective mechanisms will doubtless wait on further discovery in the etiology of these obscure maladies

II DEFENSE MECHANISMS IN DISEASES DUE TO INANIMATE EXOGENOUS AGENTS

Reference to the table that outlines a possible classification of diseases on the basis of etiology will show that the external inanimate agents of disease fall into two large groups respectively of physical and of chemical nature There are natural individual variations in the resistance of animals to agents in both of these groups The mechanisms responsible for the degrees of resistance that may occur have been investigated in some instances Most important of all is the fact that these defense mechanisms may be trained to greater efficiency and the degree of resistance thereby increased When the excitant is physical in nature the increase of resistance is referred to as a process of tolerance, habituation acclimatization training and the like when the cause is chemical, the designation tolerance or habituation is employed

A sharp distinction should be drawn between tolerance and immunity the latter term being reserved for resistance to the living agents of disease These agents differ from the inanimate in being of protein nature and therein capable of producing antibodies

Tolerance to Physical Agents

The physical agents of disease may be grouped in several categories, traumatic or mechanical thermal luminous and electrical In certain diseases a combination of agents belonging to two or more of these categories is operative

of the skin is of course a familiar instance of a protective mechanism through the production of a pigment that absorbs the ultra violet rays and thereby protects the deeper and more vulnerable layers This also is the reason for the perfect resistance of the negro to tropical sunlight (Moller)

A somewhat similar though less accentuated adaptation to the local and general effect of cold has been shown by Nansen and other explorers, who have learned to live in comparative comfort in the Arctic regions Local exposure to cold thickens the epithelium and decreases susceptibility The heat regulating mechanism of the body apparently is less able to adapt itself to unusual cold than to extreme heat

Tolerance to Chemical Agents

The tolerance both natural and acquired of animals to chemical poisons has long been known Not only are the instances of tolerance to chemicals recognized more definitely but they have been investigated more fully experimentally than have conditions of tolerance to physical agents

Some of the best studied and most interesting instances of chemical tolerance are in unicellular organisms (von Hausmann) Massart for example was able to habituate flagellates to normally intolerable concentrations of sodium chloride Davenport and Neal rendered Stentor tolerant to doses of corrosive sublimate that are four times the usual fatal concentration Ehrlich and Browning among others have investigated the drug fastness of trypanosomes a matter of vital importance in the development of Chemotherapy For example it has been found that trypanosomes can be driven from the blood in infected mice by a tolerated dose of fuchsin although not all the organisms in the body are killed The surviving trypanosomes later reappear and may again be driven to cover by a second dose of the dye stuff further therapeutic doses are however unavailing as the surviving organisms have become fuchsin fast These observations proved the necessity either of a completely sterilizing initial dose or else of a change in the therapeutic agent since the fastness is specific and does not engender a superior resistance to other drugs

There are numerous instances on record which seem to indicate that bacteria as well as animal parasites may become resistant to antiseptics but many serious attempts to demonstrate such an increased resistance have been as we know from our own experience fruitless

There are a number of striking familiar and well studied instances of an increased tolerance in human beings to narcotic poisons and drugs among which the most prominent are habituation to alcohol arsenic and morphine These conditions of tolerance to repeat differ from the true immunity to bacteria and bacterial products in that they are engendered by non protein sub

either caisson disease or seasickness In the case of mountain sickness, however, there is a delicately adjusted mechanism of protection that increases with use, as has been described by Sewall Mountain sickness is brought about by diminution in atmospheric pressure with consequent decrease in oxygen tension and is complicated by the effect of cold and perhaps to a less degree by the effect of ultra violet light (Hasselbalch and Lindhard) The body rapidly re sponds to lack of oxygen in a number of ways The red blood corpuscles are increased, frequently to as high as seven and a half millions in a few days, and the hemoglobin which carries the oxygen also is increased but somewhat more slowly Mountain sickness apparently is accompanied by an alkalosis of the blood and to compensate for this the hydrogen ion concentration, at first dimin ished may increase above normal as a result of acclimatization to high altitudes (Sundstroem) The blood flow is increased often as much as forty per cent and remains slightly increased The large mononuclear cells increase to as high as twenty five per cent the purpose of which is unknown Breathing likewise is increased in rapidity The acclimatization to high altitude decreases the CO_2 tension of the blood and causes a relative rise in the alveolar oxygen pressure (Haldane)

The adaptive mechanism in aviators apparently lies almost entirely in al tered breathing and circulation (Schneider) This acclimatization to high alti tude is the best instance available of the importance of a training process in adaptation to a new and at first harmful environment it is probable, however, that other less violent changes in environment bring into play similar mecha nisms

Excessive heat or cold produces physical disturbances in the body that may lead to definite disease The effects of heat may be local or general Local heat when applied to any part of the body gives rise to burns of varying de gree which, if sufficiently severe lead to a fatal termination Local tolerance, however may result from repeated exposure to excessive heat as in the thicken ing of the epithelium in the mouth of glass blowers and metal workers and a lessened susceptibility of the nerve endings Fuerst found that repeated heating of the guinea pig s ear to a temperature of 55° C leads to gradual thickening of the epithelium to six or eight times its original depth

The general effects of increased temperature are evident in heat stroke (hyperthermia) and in sun stroke (insolation) Individual variations exist and repeated exposure to a tolerable heat is followed by increased endurance This fact is evident in coal passers and foundry workers who tolerate heat that would be fatal for unaccustomed individuals The mechanism of this resistance is unknown and merits investigation

Other instances of the effect of excessive heat are complicated by the effect of the luminous rays as in tropical sunlight and in ordinary sunburn Tanning

stainers than in chronic alcoholics (Schweischeimer) These facts indicate greater oxidation in the tolerant individual

Arsenic Tolerance — It may be that the tolerance of the so called arsenic eaters of Styria has been somewhat exaggerated but there seems little doubt that habitues can consume from two to four times a normally fatal amount of the drug Cloetta has shown that a definite tolerance can be produced to arsenic in dogs and apparently is due to insusceptibility of the intestinal mucosa The animals die when the poison is given subcutaneously There would also appear to be an increased tolerance in other cells Adami and McCrae for example have described an active intervention of the leucocytes in disposing of arsenic in the peritoneal cavity

Tolerance to other drugs such as cocaine hasheesh nicotine digitalis and atropine seems definitely proved to exist in human beings but little is known of the mechanism involved

III Defense Mechanisms I Resistance to Diseases Produced by Animate Agents and by Foreign Proteins (Immunology)

We have endeavored to point out the great importance of that group of diseases in which the causation is known or assumed by analogy to be due to infection by some external animate agent Approximately one half of all of the diseases with which we are acquainted and so far as can be estimated over one half of the actual death are referable to agents of this nature There can be little question then as to the relative importance of the infectious diseases in any consideration of disease as a whole The importance of the infectious diseases becomes even more manifest when we consider that it is in this group of diseases that we possess the most satisfactory complete and sequential group of facts These facts not only have the advantage of completeness which renders their logical presentation possible but have led in a number of instances to practical results of the greatest importance in diagnosis prevention and cure

It would perhaps be more accurate to designate the diseases or conditions which we purpose to discuss in this section under the heading of diseases due to foreign proteins We shall find that although the infectious diseases strictly speaking are due in each instance to the entrance extension and multiplication of some living micro copic plant or animal a bacterium a spirochete a fungus a mould or a protozoan many of the condition they engender are due simply to the fact that these exogenous agents are foreign proteins Inanimate protein as well as the living tis ue from which it is derived can produce disease and lead to reaction changes of immunity and hypersusceptibility

It is not in our province in this section to consider in any detail the animate causes of disease or their modes of infection That has already been ably done

stances which are not capable of producing antibodies The condition, then is not transferable from one individual to another by means of the blood serum These non antigenic poisons are crystalloids as against the colloidal proteins Chemical tolerance differs again from protein immunity in being much less pronounced The two conditions are similar in that they are both specific

Hypersusceptibility or idiosyncrasy to drugs as well as to proteins also occurs and in this instance the analogy between the two is striking Drug hypersusceptibility may be transferred actually by the serum as in the susceptibilities to veronal iodoform and corrosive sublimate A local hypersusceptibility to drugs like strychnia and atoxyl has been described and resembles the Arthus phenomenon to horse serum No previous sensitization and no incubation period are required in these non antigenic hypersusceptibilities It is difficult to explain these conditions on any other basis than by assuming that these substances although in themselves incapable of producing antibodies are in reality ' haptenes that is to say capable of reacting with antibodies in a specific manner as a number of lipoids and carbohydrates have been shown recently to do This may be possible by their formation with a protein of a modified protein (Obermeyer and Pick Avery and Heidelberger Landsteiner) which is endowed with new antigenic properties and gives rise to an antibody that unites with both the protein and non protein moieties

Although the increased resistance that may be acquired to chemical poisons such as morphine alcohol nicotine and arsenic is definite there is by no means a settled opinion as to how it is accomplished even in those instances that have been studied most fully (Wells) The present state of our knowledge is best exemplified in a brief discussion of the most striking examples of tolerance

Morphine Tolerance — Something like twenty seven times the fatal dose of morphine may be taken by an habitue (e g 5 5 grams per diem whereas 0 2 grams usually is fatal) The organs of morphine tolerant animals are definitely more tolerant to the drug than normal The drug is excreted in diminishing amounts in the feces with increasing tolerance (Faust) and must therefore be oxidized in the body more effectually than normal (DuMez) This is shown by the fact that there is more morphine present in the brain of a tolerant than a normal animal (Rubesamen Meyer and Gottlieb) The serum of human morphine addicts contains no more protective substances for normal mice than do normal human sera (DuMez and Kolp)

Alcohol Tolerance — Although alcohol tolerance is evident in human beings where subjective effects can be judged clearly it has not been demonstrated experimentally in animals There is evidence to show that alcohol is more rapidly absorbed from the intestine in habitues (Voltz and Deitrich) The alcohol content of the blood reaches a higher level and remains longer in ab

parasites may be aided accidentally in reaching the body by mechanical wounds or abrasions. Such accidents are usual and designed in the case of protozoan diseases that are introduced into the blood by biting insects (malaria, trypanosomiasis). The need of a specific portal of entry for certain disease agents is known (malaria, gonococcus, cholera vibrio), whereas with other micro-organisms it is not necessary. The various aids possessed by pathogenic micro-organisms for overcoming the natural obstacles that represent the external means of defense of the host have been considered in the section on infection. A definite incubation period is known to be necessary before the manifestations of an infectious disease are evident. This incubation period is dependent on the rapidity of multiplication of the bacteria concerned and their pathogenicity and perhaps also dependent to some extent on the elaboration of protein splitting ferments in the body of the host (Vaughan). The animate disease agents produce their harmful effects to some extent by simple multiplication, but more particularly by the production and elimination of certain poisonous substances, which must be taken to include not only the toxins properly speaking, but the foreign proteins of which the external agents themselves are composed. The problem of virulence or pathogenicity of bacteria as bearing on infection is of fundamental importance but will be discussed only as incidental to our subject.

The infectious diseases are characterized by a group of symptoms with certain general features and presenting in each particular disease other specific characteristics. These symptoms are both local and general, depending on the degree of penetration of the micro-organisms concerned in producing the disease. We shall see later that the type and grade of immunity produced to any given micro-organism varies markedly in accordance with the depth to which the foreign agent has penetrated in the body. The local symptoms of infections are inflammations of various types dependent on the nature of the invading micro-organism and its toxins and on the particular tissue or tissues of the host that are affected. The most important general effects of an infection are fever, a disturbance in the leucocytes, usually as evidenced by their increase, and secondary results such as anemia, hemorrhage and general nutritional changes. Most characteristic of all the changes in the host as the result of invasion by an external animate agent are the immunity reactions, which have the result in various ways and in varying degrees of neutralizing the effects of the invading micro-organism.

The altered condition produced by inanimate foreign proteins is somewhat more difficult to define. In chemical constitution these proteins are at times identical with some of the plant or animal parasites which, when alive, might produce disease, but they further include chemical substances derived from any harmless living animal or plant. They differ from the micro-organisms which produce infections in that they are not living and therefore not able themselves

elsewhere in this volume (Chapter II) In the presentation of our subject, however it would be impossible particularly in view of our development of it on the basis of etiology not to have constant reference to the agents of disease and the methods by which they act

It seems unnecessary in this place to consider in detail the evolution of our knowledge concerning the nature of infectious diseases in general The earliest conception of contagion' by which Frascator (1546) explained the direct transmission of diseases, had the practical value of introducing measures of quarantine The differentiation of certain of the infections as due to indefinite miasms' was merely misleading Neither of these ideas aided directly in pointing to the real agents concerned in producing the infectious diseases The discovery of bacteria by Leuwenhoeck (1675) and their detection in wounds by Recklinghausen (1871) led first to an idea that a single micro-organism was responsible for all infections (Cohn) and this conception was replaced gradually by the demonstration of specific etiology as developed through the work of Pasteur and Koch Our data remain most complete, and the results of specific diagnostic methods and specific therapy most effective, in the diseases due to the fission fungi or bacteria It has been shown however, that both local and general infection may be caused by minute organisms of other sorts, by protozoa, including both the rhizopods (amebiasis) the sporozoa (malaria), and the infusoria (balantidium) by spirochetes (relapsing fever yaws, syphilis), by worms (bilharzia filariasis trichiniasis) by the moulds (ringworm, favus, sporotrichosis blastomycosis) by the higher fungi (actinomycosis), by the as yet unclassified group of rickettsia (typhus fever Rocky Mountain fever), and by the as yet unidentified micro organisms called "filterable viruses , or ultra microscopic organisms (rabies poliomyelitis yellow fever)

The immunity phenomena have been worked out most fully in relation to the bacterial diseases It is known however, that in type of response micro organisms in general and even harmless ones produce a reaction when they enter an animal host parenterally In virtue of their protein constitution all foreign cells are antigenic The degree of response however depends on the invading agent and particularly to what extent it invades the body The skin diseases, for example, in which the pathogenic moulds are rather superficial, do not produce profound immune reactions although the artificial inoculation of animals with these agents leads readily to antibody formation Animal parasites in general produce less marked antibody response than bacteria and correspondingly lead to a condition of tolerance rather than true immunity

The infectious diseases may be defined as due to the entrance extension and multiplication of a living parasitic agent in the animal body The entrance is effected by the parasite through the normal channels of contact with the external world as the skin and the respiratory or gastrointestinal tract, or the

tic diagnostic reactions between antigen and antibody, of which we shall later speak in detail depend for their accuracy on their essential specificity

We possess little further information on the exact nature of specificity beyond the rigorously proved relations that have just been outlined Protein chemistry is as yet unable to give us the key to the riddle of tissue differences the delicacy of its methods are at present far outstripped by the biological reactions of immunity Casein derived from cow s milk and from human milk are indistinguishable chemically the protein complexes in horse serum and dog serum are not yet separable on the basis of molecular analysis and yet in both cases immunity reactions by means of corresponding anti era will differentiate delicately b tween each of the two apparently identical substances Our present information of the chemical nature of specificity is fully and ably discussed by Wells to whom the reader is referred for further information We can treat of the matter here only in its most general aspects In general biological specificity is related to the species identity of protoplasm The injection of a microorganism identified as species A into animal B gives rise to antibodies, which produce characteristic reactions with any individual of species A but not with individual of species C or D unless species C or D be so closely related to A as to give partial or group reactions which by quantitative or ab orption methods can be differentiated In the same way the serum of animal F injected into animal B gives rise to antibodies that react only with the serum of species F Such antibodies however will be found to react not only with the serum of animal F but with the tissue extracts of animal F In other words antigenic specificity is based first of all on the protein identity of the protoplasm of the species concerned A second possibility arises It has been found that the protein constituent of the crystalline lens of the eye apparently is identical in all animals indeed i more nearly identical than is the protein of the lens in a given animal with any other tissue in that animal Consequently an anti lens serum reacts with the extract of any lens irrespective of species but not with other tissue extracts from the species furnishing the original lens There is evidence also that the specificity depends not only on the chemical constitution of proteins but on the physical arrangement of its molecules (Obermeyer and Pick) Specificity can be removed from a protein by its degradation and specificity actually can be produced by building up a protein by the reversible action of ferments or by compounding non antigenic with antigenic proteins (Gay and Robertson)

It is pos ible that the proportions and arrangement of the amino acids in a protein are responsible for its specificity An apparently simple substance like egg white can be shown to contain at least five separate antigenic units (Wells) On the other hand the antigen necessary to produce a hemolysin for sheep s cells was found by Forssmann to be contained in the tissues of several other

to invade the body and to multiply within it Their effect on the body is therefore due either to accidental contact, to artificial inoculation, or to some alteration that renders their assimilation in unchanged form from the gastro intestinal tract possible These protein substances produce disease or abnormal condition more frequently on their second or repeated introduction into the body in the condition known as anaphylaxis or hypersusceptibility, under which heading they will be discussed later

The Nature and Specificity of Antigens

The phenomena which arise in the animal body following the introduction of the protoplasm of any foreign cell whether plant or animal are evidenced by an increased power of reaction and usually are evidenced by the presence in the blood of antagonistic properties known as antibodies Conversely, any substance capable of producing such antibodies in the animal body, is known as an antigen The only chemical substances, that have certainly been proved to be antigenic are those characteristic components of protoplasm known as proteins Some evidence has been offered to show that at least two glucosides are antigenic It has been claimed also that lipoids are antigenic, but it is probable that such claims are based on the use of lipoids contaminated with proteins (Wells) The two glucosides claimed by Ford as antigenic are in the case of the one from Amanita phallades perhaps not a glucoside (Rabe), and the apparently proved glucoside in Rhus toxicodendron was not found by von Adelung to be antigenic

Lipoids and carbohydrates although not in themselves antigenic, have been shown recently to be capable of uniting with proteins in such a fashion as to produce an antibody capable of reacting specifically with either the protein or the other constituent Such non protein substances have been referred to as haptenes

So far as we are aware all proteins are antigenic provided they be in a colloidal state and soluble in the body fluids When a protein is hydrolyzed by ferment or chemical action to the state of polypeptids (Gay and Robertson) or is coagulated it loses its property of originating antibodies

Closely linked with the antigenic property of proteins is its individuality as evidenced by the specificity of the reaction between each antigen and its anti body On the existence of a specificity used in its biologic sense depends the proved etiological association of a given pathogenic bacterium with the peculiar disease that it produces And again the distinctive resistance produced by recovery from a bacterial infection or produced artificially by injection with a bacterial vaccine is specific in nature it is evidenced by an antagonism against this particular foreign micro-organism alone The character

of warm blooded animals for example fish tuberculosis does not occur in warm blooded animals and anthrax and tetanus which are characteristic diseases of warm blooded animals do not affect the cold blooded animals Certain characteristic diseases of birds rarely occur spontaneously in mammals for example psittacosis and the reverse is true since anthrax does not occur in birds And again the carnivora and herbivora have each certain typical maladies anthrax and tuberculosis do not affect dogs or rats though very fatal to cattle Bubonic plague does not occur in cattle although epidemic in rodents

The most interesting instances of species insusceptibility are in connection with many of the characteristic human diseases the exanthemata measles and scarlet fever also gonorrhea syphilis and typhoid fever never occur spontaneously in other animals and can be produced only experimentally and then in not quite characteristically human forms in such animals as are the most closely allied to man the anthropoid apes

Species immunity of this sort is rarely absolute and varies in degree with each particular case It may be evidenced in one of three general ways first by the fact that the disease does not occur spontaneously in a certain animal species although it may be produced experimentally by inoculation secondly by the fact that when experimental infection is possible relatively large doses are necessary to accomplish it and finally, in some cases relative resistance is indicated by the fact that the disease which usually occurs in a systemic form will produce when introduced into the insusceptible animal only a local lesion, e g anthrax bacillus inoculated into dogs We reserve a more complete description of the mechanism of the various types of immunity for a subsequent section but at this point it may be stated that species immunity is due in part at least to variations in the temperature of the animal concerned to variations in its metabolism and frequently to a variation in the reaction in the intestinal canal when the normal portal of entry is through this tract

Racial Immunity

Racial immunity has been noted in several well known instances where it has been found that although the species as a whole is extremely susceptible to a given infection certain varieties or races remain relatively unaffected It has been noted that Yorkshire swine do not suffer from erysipelas and that Algerian sheep rarely die from anthrax

An analogy to some extent applicable to racial immunity is perhaps the fact that certain races of mice are insusceptible to inoculations of malignant tumors although here again we are not to regard malignant tumors as infectious in origin These instances of racial immunity probably are due largely to differences in food and hygiene

animals These examples serve to show the present complexity of a phenomenon which is as important as it is inexplicable Fortunately the usefulness of the many reactions based on the reliability of biologic specificity are unaffected by an ignorance of its essential principles The facts of specificity will find an apparent explanation which has served to dull the curiosity of many in Ehrlich's famous hypothesis This side chain hypothesis, however, has been found erroneous in its fundamental assumptions, and in its further detail may be regarded as a simple restatement of fact We prefer, therefore not to assist in the perpetuation of an ingenious but on the whole erroneous hypothesis by rehearsing it except in those connections where it has aided usually through efforts to refute it in stimulating the discovery of new facts of importance

Types of Resistance and Immunity to the Infectious Diseases

The animal body possesses an elaborate mechanism for preventing the entrance and extension of pathogenic micro-organisms Even when such an external agent of disease has gained a foothold in the host sufficient to produce local or general symptoms the body continues to resist with more or less success its further advances The evolution of an infectious disease has been likened often and correctly to a battle the outcome of which depends on the balance established between the offensive and defensive forces Recovery from such infections although temporarily or even permanently accompanied by some disability may be signalized by a more or less durable and often an apparently absolute immunity against the particular infection concerned It is the chance observation of such instances of natural resistance and of acquired immunity that led to successful attempts to increase the former and to produce the latter artificially A few of these procedures succeeded through pure empiricism founded on shrewd observation and logical deduction with the rapid and continually expanding knowledge of the micro-organisms of disease and of the bodily mechanism of defense against them we have increased the instances the safety and the certainty of specific therapy of this sort

Natural Immunity

It is a matter of observation that certain infectious diseases, characteristic of one of several animal species rarely or never occur in other animals Animals of closely allied species have a certain community of susceptibility or insusceptibility to any given infection they are less likely to suffer from a disease that is characteristic of animals that are remote from them in biological series Such a condition of relative resistance is often referred to as a species immunity In a general way the infections of cold blooded animals are distinct from those

without participation of the body as a whole The clear demonstration of this condition has been given only recently, and its continued study promises to throw new light on the fundamental processes of immunity in general as will be detailed later

The fortunate condition of immunity acquired by recovery from an infection not only has been noted since the time of the ancients, but the fact made use of in a practical way Individuals who have recovered, have been used frequently as nurses in hospitals where a given infection is prevalent, e g , in plague epidemics in smallpox and in yellow fever Various efforts also have been made to reproduce acquired immunity artificially by inducing the disease in healthy people either in a modified form or in such a way as to produce a local rather than general reaction Metchnikoff gives as an illustration the observations of a Portuguese traveler in Africa, Serpa Pinto who found that the natives had discovered that they could protect themselves against the bite of venomous snakes by injecting small amounts of this venom mixed with resin under the skin It is probable that the Hopi Indians in their snake dance where they allow themselves to be bitten by rattlesnakes also have utilized a method of immunization of some sort The Moors many years ago protected cattle against pleural pneumonia by inserting a sword under the skin of a healthy animal after plunging it into the lung of an animal dead of the disease The best instance of active immunization of this sort is of course the protection against smallpox that has been produced by the Chinese and East Indians since the eleventh century ' Variolization was practiced either by inserting the scabs of smallpox pustules in the nostrils or by practicing arm to arm inoculation In a healthy individual the disease produced by this form of inoculation was usually only local and harmless but in certain instances unpleasant and even fatal results occurred The method was introduced into England by Lady Montague as a well known in 1781 and was practiced for a number of years until the introduction of vaccine by Jenner in 1798

Jenner s great discovery of the efficacy of vaccine was the result of shrewd observations and experiment but the principle on which it rested was not appreciated until the work of Pasteur Cowpox (vaccinia) represents a modified or attenuated form of smallpox although we have little more information regarding the actual nature of the virus concerned in these two diseases than had Jenner himself It had been noted frequently that milkmaids who handled the teats of cows that were suffering from a pustular eruption known as cow pox frequently acquired these pustules on their hands and it was further observed that such individuals failed to contract smallpox when exposed to the chance of infection during an epidemic Vaccination is superior to variolization because the vaccine is always available in fresh form More important still the harmlessness of the disease produced is assured not only in so far as smallpox is

Perhaps most interesting of all the forms of natural immunity is the relative resistance of certain individuals to an infection to which the majority may succumb. Such individuals have been noted since the time of Galen, and although exposed to the chances of epidemic infection and even in many instances exposed by caring for the sick, they fail to contract the disease. These instances apparently are apart from the relative insusceptibility of people that are outside the normal age limit for the disease in question. They may, in some instances, be explained by better nourishment, better health and perhaps also by certain differences in their blood, using this in an indefinite sense to indicate those protective substances which are normally present there. In general, however, individual immunity is probably not natural immunity at all, but is to be regarded as due, particularly when it is absolute, to an immunity acquired by recovery from an unperceived or forgotten attack of the disease in question.

Acquired Immunity

It has been noted, ever since diseases were identified and separated one from another, that individuals who had recovered from certain of the infections were thereafter not liable, or only rarely liable to a recurrence. This is true particularly in respect to the exanthemata, scarlet fever, measles, chickenpox and mumps, and also in the diseases plague, cholera, smallpox, yellow fever, typhoid fever and anterior poliomyelitis. Instances of recurrence in these diseases may be cases of mistaken diagnosis or may be the exceptions which prove the rule. There are other diseases of an infectious nature in which the existence of a durable immunity is impossible or difficult to state. Such diseases are syphilis and probably also diphtheria. Tuberculosis again is a disease the occurrence of which in childhood is often regarded as producing insusceptibility under normal conditions for many years or for life. In other diseases, such as those produced by the pyogenic bacteria and in gonorrhea, pneumonia, influenza, glanders, dengue fever, recurrent fever, tetanus and erysipelas, there is at least no evidence of a durable immunity, but it is probable that in some of them an actual immunity does exist for at least an appreciable length of time as is evidenced by the fact that antibodies are known to increase at the end and just after the disease and to be the cause of recovery therefrom, e g, recurrent fever and pneumonia. The existence of a temporary, though definite, immunity following recovery from an infection is extremely difficult to appreciate and is often overlooked.

In addition to a generalized protection of the body, which may follow recovery from the infectious diseases, a localized infection with an organism like the streptococcus may give rise to a localized protection of the affected part, which apparently is due to a mobilization of cells of the mononuclear type

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concerned, but also in that the possibility of transmitting concomitant diseases in human beings is eliminated It is not our purpose at this point to discuss the efficacy of vaccination which will be considered later Attempts have been made to apply this principle to other similar diseases, e g, measles and scarlet fever but no results have been obtained In scarlet fever a preventive measure of another sort is now being practiced with apparently effective results

No further knowledge of protective inoculation or further instances of similar protection were discovered from the time of Jenner until the work of Pasteur on chicken cholera in 1879 Pasteur by a combination of chance and a flash of genius found that if he allowed a pure culture of the organism that produced cholera to become attenuated he could then inoculate fowls with such cultures without producing the disease but thereby protected them against infection with that micro-organism Pasteur recognized that he had simply rediscovered Jenner s principle of vaccination and thereafter referred to his process by that name which gives us a justifiable precedent for continuing the use of the term ' vaccine for preparations of bacteria modified in various ways and utilized in the prevention and cure of disease By a similar method of vaccination Pasteur was able to prevent anthrax in sheep and later erysipelas in swine It is the same principle which has been employed further in prophylactic im munization against typhoid fever cholera and plague in human beings The next great step in the evolution of vaccination depended on Pasteur s discovery that one disease at least rabies could not only be prevented by previous vacci nation but owing to its long incubation period could actually be cured, or at least prevented from developing symptoms when treated sufficiently early We shall later consider how the work of Wright and others led to the further evolution of the principles of therapeutic vaccination even after the symptoms of the disease are manifest

Active and Passive Immunity

We have summarized briefly the condition which constitutes what is known as natural resistance or immunity and found that it varies relative to species races and individuals Secondly we have outlined the condition of acquired immunity which is produced either by recovery from a chance infection or else produced artificially These forms of immunity are strictly the property of the individual or animal concerned They have been produced in the case of ac quired immunity by a certain reaction on the part of the animal, in other words by an active participation by the animal in combating the infection con cerned We shall consider later in more detail the nature of this reaction and the characteristics of the active immunity which the animal body acquires whereas we are now dealing simply with the practical expression of this im

munity in so far as the fate of the animal is concerned As we have already mentioned the duration of active immunity acquired by recovery from an infection varies in the degree of protection it affords Recovery from certain diseases would seem to protect for life in the majority of cases, whereas in other diseases and particularly when the process is localized the protection is very temporary or actually may be marked by no apparent increased resistance It is probable even in those diseases in which durable immunity is produced, that this durability should be qualified by saying that it is effective only in so far as chance infection or infection under ordinary conditions of virulence and dose are concerned It is probable indeed that in diseases like typhoid fever where the recovery seems to endure throughout the life of the individual this is only true in cases under ordinary circumstances but does not hold true under unusual circumstances There are furthermore types of recovery connected with various conditions of relative immunity in which even the recovery is not complete The condition that is known as non sterilizing immunity , for example in many of the protozoan infections such as malaria and sleeping sickness is characterized by the fact that the antibodies produced are sufficient to kill the majority of parasites in the animal but leave a few resistant micro-organisms which subsequently are able to repeat the infection

Under usual conditions the active immunity acquired by recovery from a disease is more marked and durable than active immunity produced by artificial means There is a distinct relation between the severity of the reaction produced on the one hand by the disease itself and on the other hand by vaccination against the disease and the result produced

Active immunity may be produced by employing the agent which produced the disease modified in various ways In the first place the disease itself may be produced in modified form by utilizing the living virus which causes the disease under natural conditions The old type of variolization against small pox is an instance of immunization of this sort By choosing animals when relatively insusceptible or by localizing the point of the infection this modified disease under usual conditions may be rendered sufficiently less dangerous than the natural infection *Living cultures of bacteria have been used* in certain instances as for example in the method of vaccination against cholera in the process originated by Ferran who found that living cultures of this organism which normally produced infection through the intestinal tract could be used harmlessly for subcutaneous injections The usual method however is to employ *preparations of bacteria which have been rendered in some manner incapable of* actually producing the disease for which they are responsible This modification may be brought about by using cultures of diminished virulence as Pasteur did and this diminished virulence may be obtained by attenuating cultures through age or animal passage by heat or by desiccation (rabies) A very important

advance was made by Salmon and Smith (1886) who found that they actually could use killed bacteria and still produce immunity This latter method of a killed vaccine is now almost universally used for prophylactic purposes Another mean of modifying bacteria which not only renders them harmless but remove er ain of their toxic effects is in the form of sensitized vaccines, that is to say bacterial cultures either living or killed, that have been treated by a corresponding immune serum

Active immunity may be produced by injecting the modified preparations of cultures through various routes In the case of human beings injections are nearly always given subcutaneously for the purpose of prophylaxis although in immunizing animals injections may be given into the peritoneum or directly into the circulation Several injections are necessary, and the degree of immunity produced usually varies with the number of injections, or at least with the total amount of bacteria that is given When several injections are given the intervals between them may vary markedly The usual method has been to allow from a week to ten days between inoculations but there is reason to believe that good immunity may be produced by inoculations at more frequent intervals and even daily with the additional beneficial result of producing the maximum protection afforded in a shorter space of time Vaccines used for immunizing purposes usually are given parenterally that is to say the undigested and intact protein must reach the remote portions of the body in order to produce the type of reaction necessary The possibility of administering vaccine by mouth has been tried frequently as a less objectionable way and has been revived recently by Besredka in those infections that find a portal of entry in the intestine for example typhoid fever The same route has been used also by Calmette in immunizing children against tuberculosis It is as yet too early to draw conclusions as to the soundness of this modification

We have hitherto considered by implication at least only those forms of immunity designed to act directly upon the bacteria or micro-organisms which produce disease We know that bacteria produce harmful effects not only by their own multiplication but through their toxins and it is possible in the case of the more active of these toxins as with those of the diphtheria and tetanus bacillus to produce an antitoxic immunity by injecting the toxins themselves Antitoxic immunity must then be contrasted with or serve to amplify anti infectious immunity that we have hitherto discussed The work of Charrin and Roger and of Roux and Chamberlain (1887) was the first to demonstrate the existence of soluble toxins that may be filtered from the growths of bacteria in fluid media Roux and Chamberlain were unable however to produce an active immunity against the filtrate in the case of the diphtheria bacillus owing to its extr me toxicity and the great susceptibility of the animals they employed In 1890 Behring and Kitasato obtained better preparations of toxin

from the tetanus bacillus and from the diphtheria bacillus, and were able by modifying them by certain chemicals to inject repeatedly small amounts of them in rabbits so that they became immune. They then made use of a discovery that had been made two years previously by Hericourt and Richet who found that in the case of actively immunized animals the serum may actually be used to transfer the protection against the same infection to a normal animal. This type of transferred immunity constitutes what we now refer to as 'passive immunity,' inasmuch as the animal thereby protected is not actively concerned in elaborating those substances by which its life is preserved. Passive immunity of this sort may be demonstrated by transferring the serum from animals immunized against bacteria (anti infectious immunity) and also as von Behring showed against the toxins of bacteria (anti toxic immunity). In considering the methods of producing active immunization which we have just discussed it should be noted that the number and amount of injections necessary to protect the animal actively against a toxin are less than in instances where it is desirable to hyperimmunize the animal for the purpose of utilizing its serum for passive immunity.

Passive immunity has both advantages and disadvantages as compared with active immunity. Its advantage lies principally in the fact that it can be induced immediately in a normal individual while active immunity is a matter of days or weeks. It is inferior to active immunity in that it is never of quite so intense a degree and disappears more rapidly. Passive immunity to be most rapid and effective should be brought about in such a way as to bring the serum which transfers it to the point where it will do most good, in other words to the major point of infection. In all general infections characterized by an invasion of the blood stream either temporary or permanent passive immunity is best effected by administering the serum directly into the circulation of the host. There are certain possible dangers in such administrations which will be considered when we come to speak of anaphylaxis. In localized infections the serum is also more effective when placed near the seat of infection, as for example in the therapy against cerebrospinal meningitis where the remarkably successful results which have been attained by Flexner and others are due largely to the fact that the serum was administered intrathecally.

Early Theories of the Nature of Immunity

This brief outline of the development of our knowledge of immunity acquired by recovery from disease or produced artificially represents what may be termed the empirical state in our knowledge of immunization. There followed naturally various explanations of the striking results that have been obtained, explanations largely philosophical in nature and which could not be

expected to be ultimately explanatory in view of the limited information that was at that time available Koch (1878) thought immunity was due to some variation in the condition of the blood a rather noncommittal, though in its way accurate statement Fodor suggested further that these changed blood conditions might be due to the presence of certain antiseptic substances The exhaustion theory of Pasteur (1880) explained the acquisition of a state of resistance following recovery from a disease as due to the fact that the first growth of the bacterium in the body had exhausted the nutritive substances suitable for the growth of that particular organism, and that on second entry the same organism would find no suitable pabulum There were several objections to this theory which Chauveau pointed out and he in turn gave a theory which though opposite to the exhaustion theory was no more accurate Chauveau explained immunity by the formation of harmful substances following the first injection which prevented the growth of the organism on its returning to the protected animal It is to be noted that in both of these theories no allowance is made for the participation of the animal body in the process, which is now realized as the one essential factor in producing immunity In certain of the other earlier theories this important reaction on the part of the host is provided for as in the theory of Nägeli (1877) who thought that immunity was due to the successful struggle of the host for oxygen in competition with the bacteria Grawitz in the same way in his "excitation theory" thought immunity was due to an increased local assimilating power of cells and Buchner (1883) added another point to this idea of cell participation in noting the importance of a local inflammatory reaction in protection

The Phagocytic Theory of Immunity

Metchnikoff s phagocytic theory was the first experimentally substantiated and relatively complete explanation of immunity The protective cellular mechanism which he described remains the most important factor in bodily resistance to the infectious diseases as we understand it today The beginnings of bacteriology in so far as human pathogenesis is concerned may be traced to the demonstration of bacteria in diseased tissues It was further noted by several observers Hayem Birsch Hirschfeld and Koch that these bacteria are frequently to be found within the leucocytes and in 1874 Panum actually suggested that this inclusion might be a protective mechanism designed to get rid of invading micro-organisms The essential novelty of this explanation and its experimental proof is however to be credited first of all to Metchnikoff, who approached the subject from a novel and unbiased angle Metchnikoff had been interested in the digestive function of the mesodermal cells of sponges He found that leucocytes which are also derived from the mesoderm, take up

various particles and suggested that their function is primarily digestive About this time Metchnikoff had the good fortune to hear a lecture by Cohnheim on 'Inflammation which represented the current view of the subject namely that inflammation is a harmful manifestation rather than a beneficial process It occurred to Metchnikoff that the object or at all events the result of inflammation was to destroy the bacteria that produce it, and that the leucocytes are intimately concerned in the process of destruction of invading micro-organisms He carried out a series of experiments first by inserting thorns in the larva of the starfish (Bipinnaria) and later by infecting a small crustacean Daphnia with one of the blastomyces (Micro poron bicu pidata) In both of these instances he found that these foreign substances led to a diapedesis of white blood cells which more or less successfully surrounded and disposed of the harmful external agents These fundamental experiments then were applied to higher animals and other types of bacterial infection and led Metchnikoff to the unequivocal conclusion that the leucocytes are the most important and perhaps the solely important factors which the body possesses for defending itself against the micro-organisms of disease This theory met with considerable opposition on the part of most pathologists particularly the German pathologists although Virchow from the first expressed a favorable opinion on the subject

Let us take for granted for the moment that the activity of leucocytes is one important factor in explaining at least natural immunity leaving the discussion of the obstacles which this theory has met with to a later development With the importance of phagocytosis granted we may proceed to discuss its mechanism in more detail

According to Metchnikoff the protective cells of the blood belong to two general groups which he has called microphages and macrophages The microphages are the polymorphonuclear leucocytes which constitute from seventy two to seventy five per cent of the white blood cells and the macrophages include not only the large mononuclear leucocytes but the endothelial cells in the peritoneum in particular the bone marrow giant cells and other less well defined cells of the same type existing in various parts of the body

The studies of histologists and of immunologists during the last few years have served to amplify and render more important these fundamental concepts laid down by Metchnikoff In the first place an increasingly clear idea of what may be understood as macrophages has evolved With perfected technic and in particular with the introduction of vital (e g trypan blue) and supra vital (e g neutral red Janus green) stains relationships have been shown clearly between apparently diverse mononuclear cells widely distributed in the body and endowed with great phagocytic properties The researches of Maximow the Lewises Sabin Mallory and many others have shown that the endothelium of capillaries the mononuclear cells of the circulating blood and

expected to be ultimately explanatory in view of the limited information that was at that time available Koch (1878) thought immunity was due to some variation in the condition of the blood, a rather noncommittal though in its way accurate statement Fodor suggested further that these changed blood conditions might be due to the presence of certain antiseptic substances The "exhaustion" theory of Pasteur (1880) explained the acquisition of a state of resistance following recovery from a disease as due to the fact that the first growth of the bacterium in the body had exhausted the nutritive substances suitable for the growth of that particular organism, and that on second entry the same organism would find no suitable pabulum There were several objections to this theory which Chauveau pointed out and he in turn gave a theory which though opposite to the exhaustion theory was no more accurate Chauveau explained immunity by the formation of harmful substances following the first injection which prevented the growth of the organism on its returning to the protected animal It is to be noted that in both of these theories no allowance is made for the participation of the animal body in the process, which is now realized as the one essential factor in producing immunity In certain of the other earlier theories this important reaction on the part of the host is provided for as in the theory of Nägeli (1877) who thought that immunity was due to the successful struggle of the host for oxygen in competition with the bacteria Grawitz in the same way in his "excitation theory" thought immunity was due to an increased local assimilating power of cells, and Buchner (1883) added another point to this idea of cell participation in noting the importance of a local inflammatory reaction in protection

The Phagocytic Theory of Immunity

Metchnikoff's phagocytic theory was the first experimentally substantiated and relatively complete explanation of immunity The protective cellular mechanism which he described remains the most important factor in bodily resistance to the infectious diseases as we understand it today The beginnings of bacteriology in so far as human pathogenesis is concerned may be traced to the demonstration of bacteria in diseased tissues It was further noted by several observers Hayem Birsch Hirschfeld and Koch that these bacteria are frequently to be found within the leucocytes and in 1874 Panum actually suggested that this inclusion might be a protective mechanism designed to get rid of invading micro-organisms The essential novelty of this explanation and its experimental proof is however to be credited first of all to Metchnikoff, who approached the subject from a novel and unbiased angle Metchnikoff had been interested in the digestive function of the mesodermal cells of sponges He found that leucocytes which are also derived from the mesoderm, take up

mixed cultures of harmless B proteus and virulent streptococci together it was found that the leucocytes readily approached and took up the proteus but remained at a distance from the streptococci He found, moreover, that the toxins of bacteria frequently are associated with the negative chemotactic effect which they produce Washed tetanus spores, for instance are taken up readily by leucocytes but tetanus spores accompanied by small amounts of their toxin repel leucocytes In the case of the streptococci negative chemotaxis is accompanied also by the formation of a capsule about the organism which still further protects it from attack on the part of the leucocytes

The second stage of phagocytosis covers the actual taking up or engulfing of bacteria by the leucocytes From Metchnikoff s description one would regard this process as an active one on the part of the leucocytes Recent studies on phagocytosis ascribe the engulfing function of the leucocyte however simply to a change in surface tension a phenomenon of adsorption as first suggested by Pauli and later worked out by Barakine Phagocytosis does not mean the immediate destruction of the bacteria that have been enclosed within the leucocyte They are seen in most instances finally to disintegrate as shown by their separation into fragments and a change in their tinctorial reaction The more resistant organisms like the tubercle bacillus, may remain alive for considerable periods but finally become disintegrated within the leucocytes

The guiding thought in Metchnikoff s conception of phagocytosis has been that it is a simple adaptation of a digestive process for a purpose that happens to be of great import to the animal namely its protection against foreign cells The last stage in phagocytosis is the digestion of the bacteria that have been approached and engulfed by the leucocytes Digestive ferments have been studied by Metchnikoff and others in connection with the various unicellular organisms as in the amœba for instance and it is found that leucocytes possess similar ferments The nature of his ferment although it apparently has been demonstrated by many investigators remains even today somewhat unconvincing Buchner found that by freezing and thawing leucocytes he could obtain an extract from them which would digest bacteria Gengou found that an early leucocytic extract was more bactericidal than one which had been outside of the vessel walls for a longer period of time He further thought he could obtain a different type of ferment from each of the two general categories of phagocytes that Metchnikoff described a microcytase from polymorphonuclear leucocytes and a macrocytase from the macrocytes or large mononuclear leucocytes It seems unquestionable that the extract from leucocytes has certain digestive properties It is more difficult to prove that they are of ferment nature if we understand that ferments must be destroyed at 56 C Opie for example found two different types of proteolytic enzymes

intermediate between them the "clasmatocytes" (syn., histiocytes, tissue macrophages polyblasts) of the connective tissue are not only of common embryonic origin but are within as yet not generally accepted limits, transferable and interchangeable during adult life Together they constitute what Aschoff perhaps more conveniently than accurately, has called "the reticulo endothelial system

It was Metchnikoff's idea that to microphages was entrusted the natural defense of the body against the agents responsible for the acute infectious process as exemplified in their rapid response and accumulation in areas of acute inflammation The macrophages were shown to be active in more chronic bacterial infections such as tuberculosis and leprosy effective in disposing of protozoa and the active participants in removing other intruding animal cells including dead microphages It now appears (Gay and Morrison) that the macrophages of connective tissue are not only a second line of defense in localized areas of acute infections but are effective when the microphages are helpless as in streptococcus infections of the pleural cavity By means of a granulation tissue containing macrophages in the pleural wall of rabbits, which can be produced by indifferent agents an area of greatly enhanced resistance may be produced The accumulated macrophages moreover, can, within certain limits be moved for protective purposes to other parts of the body

As we shall see later the defense properties of both microphages and macrophages by no means are confined to conditions of natural resistance but are operative in the more significant conditions of acquired immunity, as will be explained later

The process of phagocytosis has been described by Metchnikoff and his pupils as occurring in three stages In the first stage the bacteria and the leucocytes are brought together At least they are brought together in those instances where the leucocytes are effective in making away with the bacteria and this approach of the leucocytes is brought about by a process of positive chemotaxis Chemotactic substances are eliminated by many bacteria in their growth, particularly by non pathogenic bacteria which, as a result of this positive chemotaxic influence are readily engulfed by the phagocytes It may be shown indeed that bacteria of a given species will be found to vary in the nature of the substances they eliminate as demonstrated by the action of these substances on leucocytes Bordet who was the first to demonstrate this phenomenon, showed that although an avirulent streptococcus attracts leucocytes, a virulent streptococcus repels them or in other words exerts a negative chemotaxis The diapedesis of white blood corpuscles one of the stages in inflammation and the formation of pus is the most familiar instance of positive chemotaxis Bordet further demonstrated that when virulent bacteria repel the leucocytes, they do not actually destroy them or even paralyze their activity for when he

blood cells of one animal species by the serum of another animal species, this property likewise was destroyed by heating to 55° C

These observations on the properties of blood serum led to efforts to harmonize the cellular with the humoral theory It was Hankin who first suggested alexin which is present in shed blood serum is actually derived from the leucocytes and the property of alexins simply represents an abnormal distribution of these ferments in the serum as a result of coagulation of the blood

Although it was originally suggested by the experiments of Gengou that alexin or cytase is present only in serum and not in plasma it has been shown since that plasma is fully as active as serum (Morrison) The leucocytes then cannot be regarded as the only source of alexin In fact the bacteria destroying substance that can be extracted from leucocytes as we have mentioned differs from alexin in that it resists heating to 55 C Efforts also have been made to trace the source of alexin to various organs such as the thyroid and the liver but so far no single or particular source for this substance has been determined

Natural resistance also is dependent to some extent on the presence in the body fluid of normal or natural antibodies These antagonistic substances are specific which means that a variable multiplicity each one active against a single micro-organism is present in normal serum Their mode of action will be more evident when we come to consider their exaggerated analogues that characterize active acquired immunity The method by which they are produced is not clear, but it is at least possible that they result from a subtle process of immunization due to chance organisms that have penetrated the body

The Humoral Aspects of Acquired Immunity

It is evident that natural immunity at least is due to the combined action of cells and certain properties that are present in the blood fluid whether these latter properties are derived from the leucocytes or not When we consider the factors concerned in acquired immunity the importance of the fluids becomes still more strikingly evident The great importance of certain of the factors in serum which we are about to discuss however does not controvert and indeed enhances the importance of Metchnikoff s theory of phagocytosis as we shall see later It was evident that the observations by Behring and Kitasato concerning the passive transfer of antitoxic immunity did much to point out the importance of humoral factors It may be shown further that a simple admixture of antitoxic serum suffices to neutralize the effect of its corresponding toxin No intervention of cells is necessary to explain this type of immunity

demonstrable by their activity on coagulated blood serum From polymorphonuclear leucocytes he obtained a substance designated as 'leucoprotease", which acted only in an alkaline medium to digest blood serum and was destroyed at 100° C From mononuclear cells he obtained 'lymphoprotease, active only in an acid medium and destroyed at between 55° and 78° C

The best evidences of the fact that leucocytes actually can digest or destroy bacteria are the changes undergone by the bacteria within these cells and finally the obtaining of negative cultures from such leucocytes We shall again return to a discussion of the importance of the mechanism of phagocytosis in correlating it with the developments of the humoral aspects of immunity In conclusion at this point it should be stated that according to Metchnikoff and his followers all of the destruction of bacteria and perhaps the neutralization of their toxins is directly or indirectly attributable to the action of phagocytes In other words, all immunity is cellular in nature The recent study of the more fixed cells of the reticulo endothelial system serves further to confirm this idea

The Humoral Aspects of Natural Immunity

Almost coincidentally with the early developments of Metchnikoff's theory of immunity there arose many observations that at first tended to disprove it and which led to the almost general rejection of Metchnikoff's work on the part of the German school In 1875 Fodor and Wyssokowitch found that when bacteria were injected directly into the circulation of an animal they were not eliminated through the kidney In other words they disappear somewhere within the body The observations by Fodor in the following year showed that when living bacteria are mixed with freshly drawn blood, the clotted mixture becomes sterile Nuttall (1888) carried these observations further by showing that not only blood but pleural exudate has the property of destroying various bacteria, and he found moreover that this property is lost when the blood is heated to 60° C He took pains to emphasize that this destruction is extracellular in nature and therefore not the phenomenon that Metchnikoff described Buchner (1891) still further emphasized the humoral aspects of the controversy by showing that the bactericidal action of blood is due to the blood serum, and he attributed the activity of the blood serum to the presence of substances that he called alexins (Greek alexein to ward off or protect) These alexins were destroyed by heating to 55° C but were unaffected by dilution with normal sodium chloride solution at body temperature They could be conserved for a considerable time by drying or by adding hypertonic (4%) salt solutions Buchner regarded these alexins as enzymes or ferments Daremberg in the same year described a similar destructive property for the red

of immunization Further facts elicited are that the sensitizer, or as Ehrlich later called it the amboceptor has the property of forming a union with the antigen which has given rise to it This union is so firm that the complex resists washing Bordet has shown conclusively that this union between sensitizer and red blood cell in other words between antigen and antibody must take place before the alexin (Ehrlich s complement) which ultimately produces the destruction of the cells is operative Ehrlich and Morgenroth gave a further demonstration of this fact in their experiments which showed that if a fresh immune serum is added to red blood cells at 0° C the sensitizer still unites with the corpuscles leaving the alexin in the supernatant fluid This fact is detailed because it is the discovery of this that led to a reaction of great diagnostic importance Ehrlich and Morgenroth in further elaboration of the side chain theory of Ehrlich which would explain the origin and mode of action of antibodies were led to assume the existence of innumerable complements or alexins Bordet who from the first believed in the unity of the alexin as a ferment like substance which varies quantitatively rather than qualitatively in various animals offered the following experimental proof of his contention If cholera vibrios are treated with an inactivated (55° C) anti-cholera serum they acquire a new property and become able to fix or remove the alexin from any fresh serum that is added to the mixture This fixation incidentally destroys the vibrios but the utilization of the alexin is proved by subsequently adding to such a mixture a combination of red blood corpuscles and inactivated hemolytic serum If the alexin has been fixed no hemolysis takes place This fixation of the alexin necessary to produce hemolysis by the combination of a bacterium and its antibody proved to Bordet that the hemolytic and the bacteriolytic alexins are identical or in other words there is only one alexin The importance of the reaction thus demonstrated lies in the fact that it serves to demonstrate the presence of either an antigen or an antibody when one of the two substances is known to be present Bordet himself was the first to utilize this fact, and two applications of it from Bordet s own work may be given here It may be shown that a specific sensitizer is present in the serum of known cases of typhoid fever for by adding the typhoid bacillus to such serum a combination is formed that fixes the alexin No other bacteria will produce this phenomenon with typhoid serum and no other serum than that of a typhoid case will produce the reaction with the typhoid bacillus The reaction therefore may be used in the diagnosis of typhoid fever In the second example Bordet suspected a certain cocco-bacillus that he had isolated from cases of whooping cough to be the cause of the disease He was able to demonstrate the etiological relation of this micro-organism by showing that the serum of the individuals, who were suffering from whooping-cough produced fixation with this bacillus and with no other organism isolated from their sputum The serum

Lysins — Pfeiffer (1894) found that when guinea pigs are immunized against cholera vibrio they are protected from these organisms not by an antitoxin, as he had at first supposed but owing to the presence of certain substances in their serum which have the property of dissolving the infecting micro-organisms In his experiments bacteriolysis took place only in the peritoneal cavity of an actively immunized animal or when the serum of such an animal was injected with the vibrios in a normal animal He could not reproduce the phenomenon in the test tube He therefore assumed that the serum contained some substance which is reactivated by the living endothelium The true explanation of Pfeiffer s phenomenon was not given until the following year (1895) by Bordet, who found that the fresh serum of guinea pigs, immunized against cholera, has itself the property of dissolving these vibrios in the test tube This property is lost when the serum is kept for any considerable period of time or immediately if the serum is heated for one half hour at 55° C The property in this heated serum is immediately restored on the addition of a small amount of fresh serum from a normal animal In other words bacteriolysis is due to the interaction of two substances a preventive substance later called by Bordet a ' sensitizing substance which is present in animals that have been artificially immunized, is specific in nature and relatively thermostable and a bactericidal substance which is identical with Buchner s alexin This alexin is destroyed by heating to 55 C is in itself inactive and is not increased by immunization Bordet further showed in his experiments that although this lysis could be regularly produced with fresh anti cholera serum outside the body, destruction of the vibrios is brought about by the phagocytes when the micro-organisms are injected directly into the circulation of an immunized guinea pig In other words Pfeiffer s phenomenon is to a certain extent artificial and does not necessarily represent the actual condition operative in active acquired immunity It does however emphasize a certain characteristic substance formed in the course of immunity The fact that lysis in vitro is not readily demonstrable with any bacteria other than the vibrios still further emphasizes the unusual nature of the results described

Though a partisan of the cellular aspects of immunity Bordet continued to add the most significant facts for building up of the humoral phases He found in 1898 that specific lysins like the one described for cholera were produced also by the injection not only of bacteria but of red blood cells If an animal of species "A receives injections of the red blood corpuscles of species 'B , it forms a specific hemolysin that has the property of dissolving these cells The study of this phenomenon of hemolysis has proved a most fruitful field of investigation owing to the greater ease with which the results can be observed and analyzed It resembles in all respects bacteriolysis two substances are required, the alexin of normal serum plus the sensitizer produced as the result

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been found and antibodies to them produced The bacterial "aggressins" are either identical with or similar to one or more of these less well defined toxic substances of bacterial origin They are regarded as aiding the bacterial infection in some specific manner

Another group of bacterial toxins is even less definitely known although their manifestations have long been evident These are the endotoxins described by Pfeiffer to account for the death of cholera immune guinea pigs after the injection of too large a dose of cholera vibrios Cultures from such animals are found sterile the infection is overcome although the animal dies from intoxication due to destruction of the cholera vibrios It was characteristic of these endotoxins that they were developed only in the disintegration of bacterial bodies and that they did not give rise to antibodies at least further immunization does not serve to protect the guinea pig from them This later criterion of endotoxins has been questioned by Besredka but on the whole is apparently true and if so there seems no reason to regard the endotoxin as anything more than the poison molecule of bacterial protein which, as we know from the work of Vaughan, is devoid likewise of antigenic property and therefore of specificity

The true toxins are colloidal and either protein in nature or separable with a protein fraction They are specific as regards both origin and effect in the animal body Each of them has particular affinity for some set of tissues or cells True toxins require an incubation period before their effect is evident They are thermolabile at 45 C and upwards and are destroyed by acids and oxidases The most characteristic effect which here interests us is the fact that the true toxins produce antitoxins as has already been mentioned in connection with the work of von Behring and Kitasato who further showed that the antitoxins may be transferred in the blood serum of actively immunized animals It is in connection with the formation of antitoxins in the body that Ehrlich s lateral chain theory was first introduced We know that the toxins affect certain tissues as for example the cells of the central nervous system in the case of tetanus toxin They are moreover extraordinarily active and a very minute amount is sufficient to produce symptomatic disturbances in a susceptible animal 0 000 000 33 gram of dried tetanus toxin for example will kill a guinea pig of 300 grams weight The susceptibility of different animals varies enormously, some being little affected in other words there is a definite natural species immunity to toxins When a non fatal dose of toxin is given to an animal, the animal recovers and thereafter can be given larger doses until its serum is found to contain antitoxins which neutralize the toxins not only in the animal body but in the test tube This antitoxin cannot be regarded as a simple inversion of the toxin because one unit of toxin may produce 100 000 units of antitoxin (Knorr) It is known that the body cells react to form the antitoxins because it

may be shown that after exsanguination and transfusion of an immunized animal antitoxins reappear in the blood stream Drugs like pilocarpin which stimulate cellular activity also cause increase in antitoxins We have no further information as to where any particular antitoxin is formed Ehrlich s receptor theory presupposes that antitoxin is formed in the cell that are affected by the toxins but all efforts to prove this have failed and indeed certain experiments exist, as, for example Metchnikoff s experiments with anti permotoxin which indicate that the antitoxin is certainly not formed in the cells that are acted on by the toxins

Antitoxins are of great therapeutic value the value depending absolutely on the strength of the actual product employed For this reason a complicated but accurate method of measuring the exact potency of diphtheria and tetanus antitoxins has been devised by Ehrlich Rosenau and others Such estimations must be carried out by measuring the lethal action of toxin antitoxin mixtures in guinea pigs and it is their analysis that has furnished the great stock of information on the nature and interaction of toxin and antitoxin Lately a flocculation reaction introduced by Ramon has been found to parallel neutralization as tested in animals and this simpler method eventually may replace the more complicated and expensive test But although practical results of mensuration have been achieved a difference of opinion has arisen as to the exact method by which the antitoxin neutralizes the toxin According to Ehrlich the reaction is to be regarded as a straight chemical reaction as between a strong acid and a strong base This necessitates the supposition of a number of toxins of varying toxicity and combining power in the toxic filtrate and such substances or better such diverse properties apparently may be demonstrated On analysis however all the factors that Ehrlich has described in the toxin molecule can be accounted for by assuming that various degrees of attenuation take place in a single poison (Bordet) Bordet would explain toxin antitoxin reactions as an adsorption phenomenon between two colloids of opposing electric charge This is rendered probable by the demonstration that certain of these toxin antitoxin reactions are reversible The neutralized or detoxicated mixture on injection into the animal body may be shown to liberate gradually small amounts of toxin as is evidenced by the fact that such a neutral mixture apparently containing no free toxin will give rise to antitoxins

Still another theory is the one of Arrhenius and Madsen which regards toxin antitoxin combinations as like interactions between a weak acid and a weak base This theory also accounts for the reversible nature of the reaction

Agglutinins — Charrin and Roger (1889) found that when they added Pseudomonas aeruginosa to its immune serum small clumps of bacteria occurred instead of a homogenous suspension Similar facts were noted with other sera

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Numerous theories of agglutination have been offered The most essential facts are those given by Bordet, who regards the phenomenon as physicochemical in nature and due to a process of molecular adhesion as in the flocculation of inorganic or organic colloids He demonstrated the fact that there were two phases in the reaction of agglutination During the first of these phases the agglutinin unites with the bacterium and in the second phase during which the presence of an electrolyte like sodium chloride is necessary flocculation occurs The reaction is reversible as in the case of union of toxin with antitoxin

The agglutination reaction is relatively but not absolutely specific, a property which is common to all immunity reactions That is to say whereas an antityphoid serum will agglutinate certain closely allied organisms such as Escherichia coli and Salmonella paratyphi it always agglutinates the typhoid bacillus in highest dilutions Saturation with one of the less specific organisms removes from the serum the property of clumping that organism but does not remove the property of clumping the typhoid bacillus The diagnosis of a mixed bacterial infection as with the typhoid bacillus and one of the paratyphoid bacilli may occur Such a case could be differentiated from an instance of group agglutination by saturation with each of the organisms in turn In the case of mixed infections the agglutinin for the other organism is left behind

Normal hemagglutinins either may be increased by immunization or may be produced in instances where they do not occur naturally In addition to the agglutinins active against the red blood corpuscles of another species in some animals particularly in horses and human beings isohemagglutinins occur The latter substances are of importance in the transfusion of blood which again has become a common procedure They are frequently paralleled by the occurrence of normal isohemolysins In either case it is necessary to detect such dangerous and incompatible conditions before performing transfusions

Precipitins — In 1897 Kraus found that when he added the filtrates of broth cultures of bacteria to their corresponding antisera a cloudiness occurred Two years later Tsistowitch and independently Bordet found that when an animal is given injections of the blood or the blood serum of another animal species the immune serum produced has the property of producing a cloudiness with the antigenic serum This cloudiness proceeds rapidly to the formation of a flocculent precipitate that eventually falls to the bottom of the test tube This phenomenon of precipitation is similar in most details to the phenomenon of agglutination and may be regarded as a clumping of protein molecules instead of organized cells It was discovered later that other protein antigens such as egg albumin and milk give rise to corresponding precipitins when injected repeatedly into animals of another species

Wassermann and Schutze and Uhlenhuth (1900) suggested the use of this

and their corresponding micro organisms by Metchnikoff and by Issaef In 1895 Bordet in his work with cholera vibrios in vitro noted an agglutination as well as the lysis that Pfeiffer had described He found that his agglutination occurred with even small amounts of immune serum and suggested its use as a means of identifying the cholera vibrio In the following year Gruber and Durham and Pfeiffer examined this reaction more carefully for its diagnostic value, and Widal and Grunbaum independently found that the serum of cases of typhoid fever actually has the property of clumping the typhoid bacillus in a characteristic manner This agglutination reaction is now recognized to be of great diagnostic value not only in typhoid fever but in several other diseases The phenomenon occurs whenever a small amount of an immune serum or of the serum from certain instances of disease is mixed with the corresponding organism The reaction is evidenced in the case of motile cultures first by their loss of motility and then by their collection in small clumps and a gradual settling of these masses to the bottom of the test tube It occurs not only with living cultures of the organism but with those that have been killed by heat or chemicals If the cultures are alive they are not killed by the agglutinin in immune serum and may actually proliferate but always in groups instead of as individuals At times the clumping may be thread like rather than spherical (Pfaundler's reaction) The reaction may be observed with small amounts of serum on a cover slip (microscopic method) or better in larger amounts of accurately diluted serum in a test tube or watch glass (macroscopic method)

Bacteria differ in their ability to produce agglutinins both during the course of disease and as a result of immunization Whereas such organisms as the typhoid bacillus the cholera vibrio and the plague bacillus give rise to agglutinins either during or following recovery from a disease others such as Corynebacterium diphtheriae Bacillus anthracis Clostridium tetani the pneumococcus and some of the yeasts produce agglutinins only when given repeatedly as in the courses of artificial immunization Other bacteria particularly those surrounded by a capsule do not give rise to demonstrable agglutinins In general, it may be said that motile bacteria are more agglutinogenic than nonmotile and it has been shown that separate agglutinins are formed to the flagella and to the bodies of such micro organisms The reaction is used not only for the diagnosis of disease but for the identification of a suspected microorganism as may be proved by adding it to an antiserum that has been produced by immunizing animals with a known culture of the bacterium in question Agglutinins moreover are present in certain normal sera and there are normal agglutinins not only for bacteria but for foreign red blood cells as might be suspected by analogy with the work on the lysins By repeated injections immune sera may be produced of such potency that they agglutinate bacteria in dilutions as high as one part in a million

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Normal hemagglutinins either may be increased by immunization or may be produced in instances where they do not occur naturally In addition to the agglutinins active against the red blood corpuscles of another species in some animals particularly in horses and human beings isohemagglutinins occur The latter substances are of importance in the transfusion of blood which again has become a common procedure They are frequently paralleled by the occurrence of normal isohemolysins In either case it is necessary to detect such dangerous and incompatible conditions before performing transfusions

Precipitins —In 1897 Kraus found that when he added the filtrates of broth cultures of bacteria to their corresponding antisera a cloudiness occurred Two years later Tsistowitch and independently Bordet found that when an animal is given injections of the blood or the blood serum of another animal species the immune serum produced has the property of producing a cloudiness with the antigenic serum This cloudiness proceeds rapidly to the formation of a flocculent precipitate that eventually falls to the bottom of the test tube This phenomenon of precipitation is similar in most details to the phenomenon of agglutination and may be regarded as a clumping of protein molecules instead of organized cells It was discovered later that other protein antigens such as egg albumin and milk give rise to corresponding precipitins when injected repeatedly into animals of another species

Wassermann and Schutze and Uhlenhuth (1900) suggested the use of this

reaction in the detection of human blood and in later studies, of various muscle proteins. An extensive study has shown that the reaction, however, is not absolutely specific. Closely allied species may give group precipitin phenomena, but the value of the reaction for diagnostic purposes remains unquestioned and later will be considered in more detail. A further study of the precipitins has brought out many of the facts as to the physical aspects of the antigen antibody reactions and has aided in establishing the essentials of specificity which we have already considered at an earlier point. The substance in the antigen, which gives rise to the precipitins and unites with it in the reaction, is known as the precipitinogen. The reaction is produced only when the two reacting substances are present in appropriate amounts. An excess of the precipitin, for example, or of the precipitinogen may give rise to a prezone at which point no reaction occurs. In this respect the reaction resembles the zones of flocculation and of absence of flocculation which occur between organic colloidal compounds as for example ferric hydrate and silicic acid. The stability of the colloids is changed by the ionic reaction and concentration of the added substances so that they become less stable and flocculate out. Both antigens and antibodies may occur at the same time in the serum of an immunized animal without precipitation which indicates the complexity of the reaction and the delicacy of the conditions which determine it.

Specific precipitation of this sort formed by an interaction of antigen and antibody has the property of fixing the alexin (Gay) as was also found to be true in the combination of antigen and sensitizer. This fixation reaction may be used also for the detection of either antigens or antibodies when one of them is known to be present.

Opsonins and Tropins. — Apparently we have lost sight for the moment of the importance of the leucocyte in immunity. It may be recalled that, according to Metchnikoff, leucocytes are the most important and essential factors in bodily protection against infections. There seemed little doubt in our discussion on natural immunity that phagocytes and in addition certain ferment like substances (cytases or alexins) which also may be derived from leucocytes, are responsible for the observed results. In acquired immunity it is evident that we have to deal not only with these substances that are normally present in the body, but with certain other substances known as antibodies that follow infection or immunization. We shall see later that there is evidence which indicates that even these distinctive and often very potent antibodies may be formed either by leucocytes or in those organs that produce leucocytes. There seems little question however that the powerful antibodies that we have discussed lie free in the serum. There is no definite evidence that they are artificially produced by the disintegration of leucocytes and are not free in the plasma.

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Metchnikoff was quick to interpret the interesting findings on antibodies in the light of his phagocytic theory. He first suggested that the action of antibodies was simply for the purpose of stimulating the leucocytes to the greater activity which he admitted existed in the case of acquired immunity. It was shown, however, by Denys and Leclef (1895) that although an antiserum, for example, antistreptococcus serum, does increase the phagocytosis in an immune animal or by transfer in a normal animal, the phagocytes are in no sense trained by immunization to greater efficiency. It was definitely shown that the serum affects the bacteria concerned in such a way that they are then taken up more rapidly by the phagocyte. We have then, in addition to what may be termed a simple or primary phagocytosis characteristic of normal immunity and fully described by Metchnikoff, a type of phagocytosis that may be called induced or secondary and depending on an antibody.

Induced phagocytosis, as pointed out by Denys and Leclef, was rendered more significant by the later work of Wright (1903), Neufeld, Rimpau and others. *Wright found that there are a number of micro-organisms which remain practically unchanged by the corresponding immune serum in the sense that they are not destroyed or dissolved by an immune serum, as is the case with the cholera vibrio. Such bacteria are the various cocci and the plague bacillus. Nor are these organisms phagocytized to any considerable degree under normal conditions. There is, however, a substance present in small amounts in normal serum which renders these micro-organisms more readily taken up by the leucocytes. To this substance Wright gave the name of opsonin. He regarded the opsonin as a great determining factor in infections due to micro-organisms of this group. He found, however, that this substance could be increased artificially by injections of the bacterium in question. By determining the potency of the opsonins and the demonstration of their increase following vaccination he developed a system of vaccine therapy, the significance of which we shall consider later. The same substances under the name of tropins have been described by Neufeld and his collaborators in various immune sera, and there remains little question as to the facts concerned. To recapitulate, the opsonins or tropins are substances present in small amounts in normal sera and in large amounts in immune sera which have the property of rendering the specific microorganism against which they are active more readily phagocyted. There seems on further analysis little reason to regard the tropins as any different from the immune opsonins of Wright, *although they were at first so considered.*

A Summary of the Factors Concerned in Immunity

We have endeavored to outline in the briefest possible way the factors, cellular and humoral, that are associated with the various degrees of resistance

to the infectious agents of disease It remains to attempt to explain to what extent each of these factors is responsible for protection

Regrouping the facts that we have outlined in several different ways will help to clarify our present information about immunity

Immunology has developed then two phases (1) the cellular phagocytic era of Metchnikoff beginning in 1882 (2) the study of the antibodies beginning in 1890 and now entering on a third phase (3) extension of the cellular theory by involving the fixed and semi mobile mononuclear cells and thereby explaining the origin of antibodies the nature of localized immunity and penetrating still further into the nature of acquired immunity

No one would seriously question the cellular background of immunity The animal body is not a test tube but a living reacting group of cells Cells act directly in opposing invading micro organisms and it is not simply the poly morphonuclear cells that are responsible Cells somehow somewhere form the antibodies Antibodies act directly on the invading antigens that give rise to them and such sensitized or tropinized antigens are destroyed more readily by the phagocytes Cells moreover presumably give rise to the alexin (complement) of plasma Further study lies in the direction of explaining the particular group of cells responsible for any given instance of the functions we have ascribed to cells in general

Antibodies therefore important as they are are only the reflection of processes already accomplished by the cells They have bulked large owing to their great value in diagnostic procedures through the ease of their demonstration and through their apparent multiplicity Owing to the fortunate result that attended the discovery of antitoxins therapeutic possibility has encouraged the thorough study of each successive antagonistic property as it was found in conditions of active immunity But the presence of antibodies does not guarantee protection which may occur without their presence, and antisera in general have been disappointing therapeutically

All antibodies are alike in their most important attribute namely the power of specific union with the antigen that has caused them It is easy to push the similarity further and to believe that antibodies are essentially identical, their apparent action differing only with the physical conditions under which they are operative No one would doubt that precipitins and agglutinins are essentially the same the only difference being that agglutinins clump whole bacteria whereas precipitins clump protein molecules In the same way it is easy to show that tropin and sensitizer are essentially the same Tropin activity is fulfilled by a mechanism that requires no alexin but at least normal tropin (opsonin) is increased in action by adding alexin (Cowie and Chapin) Again alexin fixation is common to sensitizer precipitate and perhaps toxin antitoxin mixtures (Nicolle) The recently established parallelism between the flocculation

of toxin with antitoxin and neutralization of the mixture (Ramon) may be evidence of the identity of the two substances

Antibodies as studied are the result of an artificial process of hyperimmunization rather than the actual condition or what may be a fully adequate protective state of acquired immunity They are moreover demonstrated largely in the test tube and do not present the actual condition of the protective mechanism in vivo

Alexin (cytase complement) is certainly a dramatically effective property of fresh serum in test tube hemolysis It is by no means certain what its action is in the living body Let us recall again the observations of Bordet on the injection of sensitized cholera vibrios in the circulating blood The bacteria were phagocyted and destroyed rather than dissolved extracellularly It may be that this ferment like substance is merely an adjuvant factor that facilitates destruction in the body and is even capable of destroying sensitized bacteria without cells when the latter are absent as in the test tube

These facts as outlined tend we believe to restrict the importance of antibodies as responsible for actual protection in conditions of acquired immunity and conversely increase the emphasis on the importance of the body cells

The relative importance of cells and fluids may be considered also by an analysis of the increasing degrees of protection to bacteria in normal and immunized animals

I *Natural Resistance*

The more mechanical methods of defense such as intact epithelium and failure to attain a suitable portal of entry are excluded from this conception Entrance of living bacteria into the body is assumed Saprophytes and weak pathogens produce localized inflammation The polymorphonuclear cells offer a first line of defense and often are in themselves sufficient to protect Alexin in the circulation may destroy individual micro-organisms that slip by the first protective line of extruded cells providing that suitable normal antibodies are present These antibodies are probably more effective in opsonizing the bacteria so that phagocytosis is increased and it is probable that alexin still further intensifies this process The macrophages of connective tissue appear in the subacute stage of inflammation and dispose of the microphages that have succumbed in struggle against bacteria and finally dispose of any surviving micro organisms

II *Enhanced Natural Resistance*

This also is possible in normal animals It is a recent concept and includes not only the various methods of localized hyperemia and venous stasis

(Bier) that have been employed in combating infections, but more particularly the macrophage accumulations that can be produced in an area by injections at a sufficiently antecedent period of indifferent substances like aleuronat and broth (Gay and Morrison) The presence of mononuclear cells (clasmatocytes) is essential to this process, and when a definite granulation tissue is produced as in the experiments of Gay, Linton and Clark, large multiples of the fatal dose of a virulent streptococcus can be disposed of

This condition probably explains most instances of local immunity and is not dependent on the formation of antibodies local or general It is probably the basis of whatever effectiveness lies in Besredka's anti virus therapy which in our opinion is not dependent on the specific nature of the broth filtrate employed (Gay[1]) The mononuclear cells once accumulated may be moved to considerable distances in the body under the stimulus of an infection at another point (Gay Linton and Clark Linton)

This type of mononuclear protection does not suffice to protect against all infectious agents as for example the pneumococcus

III *Active Antitoxic Immunity*

This is a condition operative against the soluble poisons of such bacteria as produce them e g the diphtheria bacillus It occurs as a result of immunization either artificially by the inoculation of toxin or as a result of recovery from natural infection It is due apparently entirely to the presence of antitoxins in the fluids of the body which neutralize the toxin and require no direct intervention on the part of cells

The formation of antitoxins during the process of immunization is referable entirely to cell activity The particular group of cells responsible for antitoxin formation has long been speculated on (Ehrlich) but not until recently approached in a profitable manner No final conclusions can be drawn as yet, but it seems definitely indicated that interference with the reticulo-endothelial system disturbs antibody formation in general and antitoxin formation in particular (Jungeblut and Berlot) It is the fortunate peculiarity of the reticulo-endothelial system that certain of the cells composing it, and particularly the clasmatocytes of connective tissue retain colloidal or particulate dye stuffs tenaciously Owing to this fact a partial blockade of these cells may be produced with consequent effect on their normal functions Such blockade has been found to increase or decrease antibody formation by two-thirds of the investigators that have employed the method With proper choice and combinations of blocking substances it seems quite possible that a final solution of the loci of antibody formation will be arrived at

IV *Active Antibacterial Immunity*

The building up of a condition of active immunity is signalized during recovery from the spontaneous disease or following immunization with vaccines by the appearance of one or more of the antagonistic properties in the serum which we have discussed as antibodies They represent reaction to the infectious agent but are not a measure of protection Antibodies disappear at variable periods after recovery but complete protection may persist for years as in the recovery from typhoid fever

Smallpox recovery may be associated for a time with the presence of viruscidal antibodies but immunity usually lasts a lifetime It may be true as seems experimentally the case in animals that once antibodies have been produced and later have disappeared a reintroduction of the same micro organism will cause rapid reappearance of the antibodies But even this rapid reappearance presupposes a retuning of the cells responsible for antibody formation which musts precede the appearance of the antibody

Condition of strong immunity then may occur without the presence of antibodies and even when antibodies are present it is by no means certain to what extent they are operative in the protected animal It is doubtful if bacteriolysis takes place in the blood stream and if the phenomenon of agglutination occurs in vivo (Bull) its principle purpose is to clump the bacteria in capillaries and render them more easily phagocyted Tropinization which prepares for phagocytosis certainly is of importance

The phagocytes in conditions of durable immunity are not increased in number but it is still possible that they may be qualitatively changed as indicated by at least a more rapid response to a recognized invader The polymorphonuclear cells are known to respond more actively to tropinized bacteria and they are certainly of importance in active antibacterial immunity And here again the superior function of the reticulo-endothelial cells has only begun to be appreciated An example will illustrate We have mentioned our experiments with a virulent streptococcus in rabbits An acute polymorphonuclear inflammation protects no more than normal tissue a mononuclear granulation tissue protects extremely well This tissue does not however protect against the pneumococcus but will protect against it when it has been treated (tropinized) by a trace of antipneumococcus serum The same serum treated bacteria are fatal for normal animals and in an area of acute inflammation In this connection we may recall again that antibodies are cellular in origin

V Passive Antitoxic Immunity

This is readily produced in a normal individual as a means of prevention or cure The only limitations are those of time and location In diphtheria antitoxin works most effectively when administered before intoxication has proceeded too far in tetanus, the corresponding antitoxin is most effective when given preventively or when administered into the central nervous system which the toxin specifically affects No cell participation is involved in this form of immunity

VI Passive Antibacterial Immunity

The singularly fortunate results with various examples of antitoxic therapy have led to a persistent attempt for forty years to reduplicate these results with antisera directed against more purely infectious micro organisms that is those that produce their injury largely by multiplication In other words, antiserums directed against the living agents themselves have been sought This has involved the extensive study of the antibodies we have mentioned These attempts have been singularly disappointing Antisera have been produced by hyperimmunization with the highest possible concentration of antibodies Some of them have worked in experimental infections in animals and failed in man

The one exception has been the antiserum in cerebrospinal meningitis, and the conditions under which it is operative are significant A successful anti meningitis serum must contain not only a concentration of antibodies corresponding in type to the antigen operative in the treated instance of disease but must be administered into the spinal canal where large numbers of cells (polymorphonuclear) are present The effect of this serum is recognized to be due to its tropin content

These facts have led us recently (Cay and Clark) to suggest a possible method of enhancing the therapeutic value of antibacterial sera

VII Enhanced Antibacterial Passive Immunity

This is a hypothetical condition that eventually may be realized It is suggested that the failure of antibacterial sera is due not to lack of sufficient concentration of antibodies, to failure to observe the type specificity that may exist in strains of bacteria or to lack of antibodies directed against 'humanized' (i e virulent for human beings) bacteria but simply to lack of suitable cells in the recipient to take care of the invading organisms even when they are affected by tropins These cells might simply be stimulated in the host which may

account for whatever merit was found in "leucocyte extract" and "plasmin therapy." It is possible that intact cell accumulations might be transferred from one animal to another at least of the same species. From our previous statements it is evident that better results might be expected from macrophage stimulation or transfer than from polymorphonuclears.

Anaphylaxis and Allied Conditions

There is a condition or group of conditions known as hypersusceptibility, anaphylaxis, allergy, idiosyncrasy and atopy which is inextricably connected with immunity. These terms have been used frequently synonymously and more recently, as denoting certain disputed differences in a group of conditions that have in common an exceptional increased susceptibility. In general the process in mind is due to proteins and usually is evidenced on repeated exposure to a given protein. In appearance it is the reverse of a protective or salutary phenomenon. It is alarming or even fatal, and by definition is increased susceptibility rather than increased resistance. And yet the fundamental causes of anaphylaxis and immunity may be the same. Although instances of this unusual condition have long been recognized in disease and also in the process of immunization, no comprehensive idea of it existed until relatively recently. It had never been explained why animals that were being immunized with bacterial products began to waste away and die of what we were pleased to term cachexia. It was never understood why certain individuals are given symptoms of acute poisoning by eating some foods, such as eggs or strawberries. Other individuals show extreme local susceptibility to iodoform. Sufferers from hay fever and asthma are thrown into attacks resembling acute coryza or bronchial spasm under conditions which only faintly were appreciated. Finally there are the extraordinary group of symptoms known as serum sickness, which follow the repeated dose or sometimes the initial dose of a foreign therapeutic serum, and which are manifest either by acute symptoms of vomiting, dyspnea and collapse, or by delayed symptoms of joint pain, fever and a rash.

We have seen how the study of the antibodies produced by the injection of harmless proteins finally came to explain much of the mechanism of the reactions of immunity that first attracted our attention in connection with bacterial proteins. The same history has been true in the development of our knowledge of anaphylaxis, only in the latter case the first well studied instances were in connection with the harmless proteins. Isolated observations by Magendie (1839) and by Flexner (1894) were not appreciated as representing a widespread and fundamental condition in animals that may be induced by a previous administration of any foreign protein substance. It remained for Richet (1902) who was working with a poisonous protein of shellfish, to show

that dogs may be rendered more susceptible than usual to a second injection of this substance through having received a previous one. For this reason he gave the name of anaphylaxis to the condition as opposed to the condition of prophylaxis which ordinarily follows repeated injections of a protein under the guise of immunity. It may be stated at this point that increased susceptibility may be produced by any substance that gives rise to increased resistance provided the dosage and intervals between injections is spaced properly. The exact relation however of increased susceptibility to an increased resistance is by no means understood. It may be a parallel condition that is independent of the condition of immunity or, on the other hand, it may be simply a stage in the development of immunity. The best we can do at the present time is to outline the conditions under which anaphylaxis occurs.

Following the work of Richet two general phenomena were discovered in animals which illustrate directly the two general forms of anaphylaxis as we now understand them, a local form and a generalized form. In 1906 Arthus found that rabbits that had received several injections of horse serum finally respond to a subsequent injection by a local sterile necrosis at the final point of inoculation which may be remote from previous injection areas. This evidence of local anaphylaxis never occurs in normal rabbits. An exactly similar condition has since been described by Lucas and Gay in children who were given repeated doses of diphtheria antitoxin. The second or generalized form of anaphylaxis was discovered independently by a number of observers in connection with the testing of diphtheria antitoxin. It was found that guinea pigs that had received a minute amount of a toxin antitoxin mixture subsequently were fatally intoxicated by injections of a relatively large amount of antitoxin or of normal horse serum. This form of anaphylaxis also occurs in human beings in the condition known as the accelerated serum reaction that may follow immediately on the injection of antitoxin or any foreign normal serum.

The study of these phenomena of generalized anaphylaxis in guinea pigs and the analogous phenomena in other animals have given us most insight into the mechanism of the process in general. Certain of the more important facts should be outlined. A very small amount of a suitable protein, whether it be a bacterial protein and therefore somewhat toxic or a harmless protein such as milk, serum or egg white, will so alter the physiology of a normal guinea pig that its reaction to a subsequent injection of the same substance becomes radically and often fatally different. This specific sensitivity to the protein in question remains either for a long period of time or for the entire life of the animal. On receiving a second dose of the same protein an animal reacts characteristically, the rapidity of the reaction depending on the route chosen for administration of the protein and the amount of it. The animal shows symptoms of excitement followed by paralytic symptoms, which latter phe-

nomenon is particularly significant in the form of a respiratory distress which often brings about death through asphyxia. Anaphylaxis is as specific as immunity. An animal sensitized to one protein reacts within group limits only to the same protein and an animal may be sensitized to several proteins and react separately to each one of them in turn. When a protein is hydrolyzed to the point that it fails to produce immunity, it likewise ceases to produce hypersusceptibility. Anaphylaxis as studied in the guinea pig may be transferred by means of the serum and is therefore inherited also by the first generation of the offspring. Death, which may occur within three to five minutes if the second dose is given intravenously, is preceded by the stormy symptoms that have been mentioned and at autopsy characteristic lesions are found (Gay and Southard). These lesions are an insufflation of the lungs produced, as was subsequently shown by Auer and Lewis, by paralysis of the bronchial musculature, and secondly minute hemorrhages in various parts of the body, particularly in the stomach, caused by fatty degeneration in the capillary endothelium. The phenomenon of anaphylactic shock in the guinea pig at least and in the dog is primarily intracellular in nature, as was first pointed out by Gay and Southard and later confirmed by Weil, Manwaring and others. Individual muscular organs of a sensitized animal, such as the heart and the uterus, may be shown to be more irritable than normal when subjected to a fluid containing the protein to which the animal is sensitive.

The extreme symptoms that occur in the guinea pig are by no means equally prominent in other animals and there are certain other criteria of anaphylactic shock, one or more of which may be found in practically all animal species that have been tried. These characteristic symptoms are a fall in the blood pressure, a fall in temperature, delayed coagulability of the blood and, last of all, a falling in the alexin content of the blood serum. The mechanism on which the shock depends, although intracellular in the guinea pig and dog, is probably extracellular in origin in the rabbit. Anaphylactic shock can be produced in the white rat only when the diet has been restricted (Seegal and Khorazo).

Numerous theories have been devised to explain the facts already obtained and they have been useful in leading to further experiments. The earlier theories of Rosenau and Anderson and others regarded the reaction as due simply to an interaction of antigen and antibody. In the theories of Gay and Southard, Vaughan and Wheeler, and Besredka, there is evidence which goes to indicate that the substance in a protein which gives rise to sensitization to that protein is not the same as the fraction of the protein that produces the intoxication. The idea is expressed most concretely in what may be regarded as the best of several proteoclastic ferment theories of anaphylaxis, the one offered by Vaughan. Sensitization is regarded as originating or increasing the

proteolytic ferment in the serum and this ferment splits the protein rapidly on its second introduction into the animal body and discloses the poison molecule within it. The poison molecule may be uncovered artificially in vitro by splitting the protein with alkali alcohol. This theory is essentially corroborated by the experiment of Friedberger who demonstrated an "anaphylatoxin", when the serum of a sensitized animal was brought in contact with the antigen.

A further development of these ideas is expressed by the adsorption theories of anaphylaxis. These theories, although admitting the formation of a toxin under the conditions just noted, would attribute the substrate from which this toxin is obtained to the serum of the host rather than the antigen. This theory, which has been developed by the work of Keysser and Wassermann, by Bordet and Zunz, and by Jobling and Peterson, attributes the liberation of the toxic substances from the antiserum to an adsorption of the antiferment in such serum, thereby allowing the ferment present in it to act upon its own protein.

The taraxin theory that has been offered by Novy and De Kruif to explain anaphylactic shock would explain the intoxication as due to a tautomerization of the blood proteins, by a process similar to blood coagulation. Protein cleavage is not affected according to Novy and De Kruif, but any substance, even distilled water, when added to serum may bring about this change in the arrangment of the molecules in the protein. Anaphylaxis is specific only in the sense that the combination of antigen and antibody acts best as a catalyzer to bring about this change of molecules.

Animals that recover from anaphylactic shock are thereafter for a period of time insusceptible to reintoxication by the protein to which they have been sensitized. They are spoken of as being in a condition of anti-anaphylaxis or in a refractory stage. The latter term indicates the fact that they eventually become sensitive again to intoxication. This condition of anti-anaphylaxis is of practical importance since it can be induced artificially by using relatively small amounts of the antigenic substance, with the advantage that the animal or individual may then be given any amount of the protein without harm. In the case of serum, anti-anaphylaxis (or desensitization) is produced by giving small amounts of the substance subcutaneously or by the rectum. When it is desired to administer large amounts of serum therapeutically directly into the circulation, desensitization can be accomplished by giving a very small amount of the substance intravenously, or simply by injecting the therapeutic dose very slowly. Hypersusceptibility to therapeutic serum, usually horse serum, should be tested for by means of a local reaction which will be considered later. An "anaphylactoid" reaction resembling in many respects true anaphylaxis may be produced by the initial injection of non-protein colloids such as agar, gum acacia, or the colloidal metals (Karsner).

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Allergy and Anaphylaxis in Man

The study of anaphylaxis in experimental animals has been essential in recognizing various aspects of the condition and in learning something of its underlying mechanism. It will continue to offer a major and profitable interest to many investigators. It is however in human beings that the protean aspects of this reaction-complex are at once most diverse and interesting. The human body is indeed illustrative of all types of the hypersensitive reaction to which we have referred and the increasing knowledge of the essential criteria of these states in recent years has cleared up many obscure conditions.

Allergy (changed activity) is perhaps the caption under which to collect many human hypersensitive phenomena. Anaphylaxis is used for those instances that parallel the animal reactions to well defined protein like serum and atopy (strange disease) has been employed by Coca and Cooke to designate hereditary conditions of asthma which were thought not to be due to an antigen antibody reaction. An appreciation of the multiplicity of hypersensitive phenomena has reached the state where we have not only specialists and special clinics for these maladies but special journals and societies for their discussion.

For the purpose of orientation we may present the recognized human manifestations of hypersusceptibility from two different view points (1) the area of the body involved in the manifestations and ( ) the materials that give rise to the conditions.

Reactions of hypersusceptibility like infections involve increasingly extensive areas of the body. The skin is involved either alone or in combination with other areas in some of the most characteristic conditions of allergy. We find first of all drug idiosyncrasies to such chemical substances as iodoform antipyrine quinine formalin and some arsenicals like salvarsan rather severely irritating phenomena that are usually classed as anaphylactic but with no very clear understanding as to how they are produced. These substances are non protein and therefore non antigenic but it may be that like certain carbohydrates or lipoids they can unite with the proteins of the hypersensitive individual to form a new antigenic complex. At all events redness itching and edema of the skin follow exposure in instances of this sort. The more clearly defined skin conditions angioneurotic edema eczema urticaria are referred to frequently nowadays as allergic in nature without any clear idea as to the inciting agent which may however be a simple chemical substance such as those mentioned. There is evidence also of a specific susceptibility to various physical agencies such as light heat and cold (Duke) which is predominately characterized by urticarial eruptions. Another skin manifestation of hyper

proteolytic ferment in the serum and this ferment splits the protein rapidly on its second introduction into the animal body and discloses the poison molecule within it This poison molecule may be uncovered artificially in vitro by splitting the protein with alkali alcohol This theory is essentially corroborated by the experiment of Friedberger, who demonstrated an 'anaphylatoxin', when the serum of a sensitized animal was brought in contact with the antigen

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of reaction frequently are due to hereditary asthmatic tendency or status lymphaticus in children, rather than to a sensitization by previous injection of serum as in the guinea pig (Park) At all events alarming symptoms on first injection of serum may not be expected in more than 1 in 70,000 and death is estimated to have occurred in 1 out of 50 000 The reactions in this group are agreed to be in the nature of combinations between antigen and antibody They parallel at least in many instances the precipitin reaction and may be identical with them Alexin fixation occurs with anaphylactic shock of this kind as in other antigen antibody reactions

Food allergy is probably a much more wide spread phenomenon than has been recognized The cyclonic gastrointestinal symptoms that follow the ingestion of egg white in certain children and shellfish or berries in adults are only the more emphatic instances of hypersusceptibility to foods The causal relation is much more difficult to discern when common food stuffs such as wheat egg and milk give rise to less definite symptoms such as urticaria angioneurotic edema eczema migraine asthma and indefinite abdominal pain with distention constipation or diarrhea According to Rowe these common instances of food allergy frequently are not detected by skin tests and are evident only on cessation of symptoms following dietary trial

The predominatingly respiratory conditions of allergy follow simple inhalations of inconceivably small amounts of pollen dusting powders like orris root emanations or ' dander from the hair and feathers of animals and birds and even such materials of animal origin as glue

Bacterial proteins can give rise experimentally at least to specific hypersusceptibility and anaphylactic shock It is as yet uncertain to what extent a similar process is operative in chronic or repeated bacterial infections in man The essential phenomena of such diseases as scarlet fever coryza and acute articular rheumatism diseases of recognized or suspected bacterial origin have been explained recently and on reasonable grounds on the basis of allergy The familiar skin reactions to tuberculin mallein and the toxin of scarlet fever are certainly instances of allergy

The Application of the Principles of Immunology in the Diagnosis Prevention and Treatment of Infectious Diseases

Interesting as are the facts of immunology viewed abstractly as constituent parts of a biological science they become more compelling when viewed from the standpoint of their practical utilization The guiding impulse that has provoked the enormous volume of work in this field during the past forty years very properly has been utilitarian So strong indeed has this impulse been that not infrequently it has led very naturally to hasty and unwarranted

susceptibility is the Arthus phenomenon which may occur in man as well as animals under the new exceptional condition of repeated doses of a foreign serum It is characterized by necrosis at the final point of inoculation

The respiratory system is involved characteristically in man not only as a localized demonstration of a general anaphylactic effect as in the serum anaphylaxis of guinea pigs but also as a localized reaction to specifically acting substances that come in contact with the mucous membranes of the nose and throat The diseases known as hay fever and as asthma are produced not only by the pollen of various plants but by a variety of substances in the form of obvious dust and even in the so called emanations or effluvia of animals

The gastrointestinal tract is involved primarily in the acute symptoms produced by the ingestion of various food stuffs such as egg white milk berries and fish that although normally acceptable pabulum for the great majority, may severally call forth in the exceptionally sensitive individual nausea vomiting colic diarrhea and more indefinite chronic abdominal distress

A generalized reaction involving any or all of the symptomatic disturbances in skin respiratory tract and gastrointestinal tract follows the parenteral inoculation of a foreign protein such as horse serum in one who is specifically sensitive to it

A survey of the various conditions and materials that give rise to hypersensitive manifestations is another way of presenting the extraordinary breadth and significance of these phenomena

Duke has shown that certain individuals are sensitive to one or more physical agents such as light heat cold scratching burns and freezing Such individuals exhibit not only local manifestations in the skin in the form of urticaria and edema but also show asthmatic and abdominal symptoms In short all the manifestations produced in other individuals by the use of foreign proteins may be invoked A further study of these conditions may aid eventually in explaining the mechanism by which the various non antigenic drugs to which we have referred produce their idiosyncratic effects To these drugs may be added the marked individual susceptibility in this case a widely distributed one to the oleoresins in poison oak ivy and sumac

Foreign proteins may be primarily toxic when injected parenterally into man or animal in virtue of their hemolysins as in foreign animal serum or some other toxic substance as in the actinian poison that Richet employed Horse serum also produces a delayed reaction in human beings in the nature of urticaria and joint pains that occur several days after injection (v Pirquet and Schick) More striking and serious however is the accelerated reaction that occurs either on the first or at times only on repeated injection of this alien protein All the symptoms of guinea pig anaphylaxis may follow, including in rare instances, the fatal termination Apparently the severer types

a known immune serum Thus in the case of typhoid fever or paratyphoid fever it is necessary not only that the organism isolated in the circulating blood or stools should conform morphologically and in its reaction on culture media to recognized typhoid or paratyphoid bacilli but that it should become agglutinated in a characteristic manner by an antiserum that has been produced artificially by immunization with identified strains of the organism in question In certain instances it may be possible to use serum from a case that is known to be suffering from the disease in question The reactions between the suspected organism and the known immune serum that may be used are first of all the agglutination reaction and second the alexin fixation reaction and in the case of the cholera vibrio Pfeiffer's phenomenon of bacteriolysis as produced either in the animal body or in the test tube A precipitin reaction between a filtrate of broth culture and the corresponding immune serum may serve also as a diagnostic procedure

The second useful application of reactions of this sort lies in the determination of the etiological relationship of a newly discovered organism that is suspected to be the cause of a disease as shown by its reaction with the serum of patients suffering from that disease We have already given an example of the usefulness of such a test in connection with the bacillus isolated from whooping-cough by Bordet and Gengou These authors found that the coccobacillus gave a positive fixation reaction with the serum of whooping cough cases whereas controls with normal serum and with the patient's serum and other bacteria were negative The dysentery bacillus was shown by Shiga to be the cause of the disease because it alone of the intestinal bacteria reacted with the patient's serum

Further use of tests of this sort lies in the separation into types of bacteria of the same species This test is useful not only for the purpose of classification but for the practical purpose of determining the exact variety of a given microorganism that may be responsible for an individual instance of disease An example of the latter usefulness is the determination of the particular type of pneumococcus concerned in each case of lobar pneumonia where such a determination is essential in order to produce the rigorously specific immune serum which alone may give results in therapy Similar tests have also been applied to the type differentiation of the meningococcus Three types of Bacillus botulinus have been determined and the toxin of each is separate There are a number of immunologically different types of the diphtheria bacillus but fortunately their toxins are identical and a monovalent antitoxin will neutralize them all Again agglutination tests have served to differentiate between the hemolytic streptococci that are concerned in scarlet fever and those in erysipelas and other diseases

A known immune serum may be used in a variety of other ways for the

conclusions. There is no branch of scientific medicine that has been more liable to exploitation and injudicious enthusiasm; no literature is more clogged with half-baked theories and unrealized expectations. The rewards have been actually so great that too many and too wide-reaching results have been expected. There is no reason why proper enthusiasm as to the possibilities of specific diagnosis and therapy should be abated in the least, but we may look forward to many years of patient endeavor before the ultimate realizable result is attained.

In the few remaining pages an effort is made to tabulate the practical results that have been obtained in the diagnosis, prevention and cure of disease through the utilization of the principles of immunology that have been outlined.

Diagnostic Reactions of Immunology

The diagnostic value of the various phenomena that occur in connection with conditions of immunity depends on the production of the changed reaction, and frequently on an extracellular antibody formation representing this changed reaction in the body of infected or immunized animals. The diagnostic tests with the serum of such animals depend on the specific property that antigens have of uniting with their corresponding antibodies. When either of these two substances is known to be present, the existence of the other may be determined. We may therefore readily divide this discussion into two parts: (1) a consideration of the tests for presence of an antigen by employing a known antibody, and (2) the tests for a suspected antibody in the presence of a known antigen.

Tests for Suspected Antigen in the Presence of a Known Antibody

In reactions of this sort the antibody usually is furnished by the serum of a hyperimmune or artificially immunized animal, in other words, an animal in which the antibody content has been raised to the maximum. In this and the following subsections we shall make no attempt to describe the technical procedure necessary to demonstrate the substances that are being sought for. A description of the methods of procedure, the causes of error, the criteria of what constitute a positive reaction and the like will be found in recognized textbooks of immunity, notably in those of Zinsser and of Kolmer. We have space here simply to indicate the scope and the relative value of the different varieties of reaction that have been shown to be useful.

The identification of suspected bacteria is one of the important uses to which a known antiserum can be put. When micro-organisms are isolated from the body in pure culture it is necessary to identify them not only by their cultural characteristic but ultimately by their specific property of reacting with

a known immune serum This in the case of typhoid fever or paratyphoid fever it is necessary not only that the organism isolated in the circulating blood or stools should conform morphologically and in its reaction on culture media to recognized typhoid or paratyphoid bacilli but that it should become agglutinated in a characteristic manner by an antiserum that has been produced artificially by immunization with identified strains of the organism in question In certain instances it may be possible to use serum from a case that is known to be suffering from the disease in question The reactions between the suspected organism and the known immune serum that may be used are first of all the agglutination reaction and second the alexin fixation reaction and in the case of the cholera vibrio Pfeiffer s phenomenon of bacteriolysis as produced either in the animal body or in the test tube A precipitin reaction between a filtrate of broth culture and the corresponding immune serum may serve also as a diagnostic procedure

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A known immune serum may be used in a variety of other ways for the

determination of suspected antigens The various forensic tests are instances of the usefulness of reactions of this sort The human origin of blood stains or semen stains may as we have intimated already, be accurately determined by means of precipitin reaction carried out by adding a known antihuman serum from the rabbit to dilutions of the suspected blood or solutions of blood stains Apparently an antiserum to semen is specific not only for the animal species but for semen as against blood Lens proteins in all mammals birds and reptiles apparently are identical or organ specific rather than specific Thyroglobulin is also characteristic of the organ Abnormal proteins, characteristic of disease as the Bence Jones protein in multiple myeloma is detectable by a specific precipitin reaction

The same reaction may be used also to detect the falsification of meat as in the case of sausages that may be labeled pork but found to contain horse meat or other meat It is further applicable in the detection of violation of game ordinances as in the instance described by the author[1], who could prove the presence of venison in the possession of a suspected individual who claimed that the meat was veal The precipitin reaction usually is employed in tests of this sort, but the reaction of alexin fixation as described by Neisser and Sachs is even more delicate for the purpose

The diagnosis of any particular bacterial infection rests when possible on the isolation of the micro-organism concerned from some local lesion or from the circulating blood It is possible however in some diseases to demonstrate the presence of protein substances derived from the bacteria even when the bacterium itself is not readily isolated It may be shown, for example, that the precipitinogen of the pneumococcus is present in the urine and in the sputum of cases of pneumonia and the variety of pneumococcus that is concerned may be determined by the precipitin test with the appropriate immune serum The spleen of rats that have died of plague can be shown to contain protein of the plague bacillus by adding antiplague serum to an extract of such organs The diagnosis of anthrax in the organs of cattle that have died of the disease may be determined even when considerable decomposition has taken place by means of a thermo precipitin test that is to say, by demonstrating the presence of a precipitinogen that resists boiling

It would lead us too far afield to more than mention certain other studies in which the precipitin and allied reactions have been put A determination of relationships in the animal kingdom has been interestingly shown by Nuttall who studied the forensic precipitin test The absorption of intact foreign proteins from the intestinal canal in infancy and their detection in the blood has wide implications in infection and immunity A specific precipitinogen in plants infected with mosaic disease as recently shown by Purdy, may have wide significance in explaining the filterable viruses

Tests for Suspected Antibody in the Presence of Known Antigen

In a number of the acute infectious diseases the malady is characterized by the appearance in the blood of the patient of the so-called ' antibodies ' to the recognized agent of the disease in question The detection of what particular antibodies are present is of pre-eminent and persuasive diagnostic importance The success in obtaining a positive reaction between a patient s serum and the agent of the disease concerned depends largely on the antigenic capacity of the micro-organism the area involved in the infection and the duration of the disease itself In very acute diseases as plague for example, recovery or death usually occurs before antibodies are detectable but in other more lasting infections such as typhoid fever, antibody formation occurs early enough to be of great service in diagnosis The reactions employed in these tests are the agglutination reaction the fixation reaction and in rare instances the conglutination reaction Mixed infections can be detected as well as single ones if Castellani s method of agglutinin absorption is employed With correct technic there is little danger of misinterpreting positive results The occurrence of typhoid fever in typhoid vaccinated individuals which latter process in itself gives rise to agglutinin formation although puzzling can be ascertained by correct technical methods

The agglutination reaction has been shown to be of pre-eminent value in the detection of typhoid and paratyphoid alpha fever No diagnosis of these diseases is finally complete until confirmed by this method Among other diseases in which this test is of value are Malta (undulant) fever, a disease far more prevalent than originally assumed and with interesting relations to contagious abortion of cattle Tularemia is characterized not only by the presence of agglutinins for Pasteurella tularensis but by their extraordinary persistance The agglutinin test is also of value in relapsing fever and glanders in horses The persistance of agglutinins after recovery in diseases like typhoid fever may indicate the carrier condition

The agglutinin reaction is of distinct though more limited value in the diagnosis in paratyphoid beta infections in bubonic plague in whooping cough in sporotrichosis in cerebrospinal meningitis in pneumonia and in bacillary dysentery The reaction has been tested in many other infections but with no general acceptance of its usefulness

The reaction of alexin fixation is of great value in glanders and in syphilis in which latter case it is used in essential form although with modified principle in the Wassermann reaction The precipitin test (Kahn) seems to parallel the fixation reaction for syphilis closely

The fixation reaction is of some value in the diagnosis of the following

infections typhoid fever tuberculosis bacillary dysentery, gonorrhea (chronic forms) whooping cough plague thrush, relapsing fever and echinococcus disease

The passive transfer of anaphylaxis has been suggested as of value in a few diseases such as tuberculosis and cancer, but has not been utilized generally

A number of these tests have been employed erroneously after vaccination with bacterial vaccines to indicate whether the patient is actually protected It should be recalled that antibodies are indicative of reaction rather than as a measure of protection which latter condition implies cell preparation

There are a number of other tests of suggestive or actual value in the diagnosis of infections that are dependent on some metabolic change in the individual that is reflected in certain of the physical properties of the blood serum Such for example is the epiphanin reaction of Weichardt which depends on the change in diffusion produced by a combination of an antiserum with its antigen Of similar nature is the meiostagmin reaction of Ascoli dependent on a change in surface tension as measured by the size of drops of a mixture of antigen and antibody as compared with a control mixture and measured by a stalagmometer The reaction has been claimed to be useful in tuberculosis and typhoid fever Other tests have depended on the increased globulin present particularly in the cerebrospinal fluid as in the butyric acid test of Noguchi, and in Lange s colloidal gold test which is based on precipitates with the spinal fluid in different zones corresponding to various degrees of involvement of the central nervous system in syphilitic and other processes The Abderhalden test for proteolytic ferments in the blood suggested as a means of diagnosis of pregnancy, is of little value in the diagnosis of infections owing to its non specific character

The exact measure of the concentration of antibodies in the serums of hyperimmunized animals employed for preventive and therapeutic purposes is very important The antitoxin content of antiserums to toxins of diphtheria, tetanus venom, botulism gas gangrene and even cholera and dysentery are generally accepted as measuring correctly the value of such preparation in preventing or curing the respective intoxications in experimental animals They do not necessarily mean that such antitoxins will actually work therapeutically in these diseases in man for reasons that later will be specified Antibacterial sera as for example against pneumococcus and meningococcus also are standardized either directly on animals or by their content in antibodies Here even more human therapeutic experience is at variance with the experimental findings

Here probably for the sake of completeness should be mentioned the diagnostic tests for compatability of human blood types essential to avoid the occurrence of isohemagglutinins and hemolysins in transfusions The interest

in these studies extends into the field of genetics in determining racial type predominance and possible presumptive tests for paternity

Diagnostic and Prognostic Allergic Tests

Of great diagnostic and prognostic value are the allergic tests demonstrable in man and animals on the local application of known antigens to localized areas of the body usually to the skin or on the conjunctiva The reactions vary markedly in their appearance and their import, but may be grouped as follows

Hypersusceptibility to drugs pollens food stuffs and foreign proteins is evidenced by a reaction on intradermal inoculation which takes place in a few minutes and is characterized by redness itching bleb or urticarial wheal and soon disappears

In the Schick reaction for protection against diphtheria the normal individual who is susceptible to the disease gives a positive area of redness and infiltration in twenty four to forty-eight hours after intradermal injection of toxin When insusceptible to diphtheria no reaction occurs The Dick test is similarly negative when resistance to scarlet fever is present but differs from the Schick test in that a sensitization to the scarlet fever streptococcus proteins seems to be necessary before the individual becomes susceptible that is positive to injection of the toxin No reaction (insusceptibility) occurs in young infants followed by reaction (hypersusceptibility) in later years of child hood followed in turn by a second insusceptibility after recovery or immunization with toxin

Another series of allergic tests are employed largely for the diagnosis of infections such as the tuberculin test and the streptothricin test the latter serving to differentiate the latter infections from those due to the tubercle bacillus (Claypole) These tests do not necessarily mean an active process but simply that localized infection has taken place and may be indicative rather of a reactive and actually mildly protective condition Mallein and abortin are employed in glanders of horses and contagious abortion of cattle to diagnose the disease Luetin as proposed by Noguchi has not been generally accepted as of value in determing syphilitic infections All these tests differ in general appearance from those described in being slower in appearance and more indurated

As a well authenticated test of protection may be mentioned the allergic reaction to smallpox vaccine which occurs in twenty four hours in those individuals who are protected against the disease and who moreover will fail to give a positive vaccinia or vaccinoid postule (Jenner Force and Stevens) Of similar import is the typhoidin reaction of Gay and Force which, in spite of

infection typhoid fever tuberculosis, bacillary dysentery, gonorrhea (chronic forms) whooping cough plague, thrush relapsing fever and echinococcus disease

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symptomatic anthrax or black leg in cattle and in man cholera plague typhoid and the paratyphoid fevers In none of these instances does vaccination insure as advantageous or complete a protection as does recovery from the disease, but none the less the employment of preventive vaccination has passed the experimental stage

Less definite but very encouraging results by preventive vaccination are reported in the infectious abortion of cattle and of horses and in tuberculosis of cattle In man the prevention of whooping cough and of dysentery by previous introduction of their respective micro-organisms are worthy of further consideration as are also the promising results obtained by Calmette in the immunization of infants against tuberculosis by the ingestion of bile treated tubercle bacilli

In a still further group of diseases where considerable trial has been made there is sufficient suggestion of favorable results to merit further investigation Canine distemper may possibly be prevented by a vaccine of the B bronchi septicus Experimental syphilis in monkeys and even in man may be prevented according to Metchnikoff by the use of a modified virus It has been claimed recently that poliomyelitis in monkeys may be prevented by intradermal injections of the virus Meningococcus and pneumococcu infections perhaps may be minimized by previous injection of the causative organisms The treatment of common cold by a mixed vaccine obtained from the respiratory tract has many adherents but whatever success may be obtained must in the absence of any proved etiological agent in this diseas be attributed to a non specifi form of protein stimulation to which reference will be made later

Vaccine prophylaxis has been attempted in a number of other infectious diseases for the most part sporadically and here again the question of an etiological agent has in such diseases as influenza and yellow fever made us justifiably skeptical of the significance of the results reported

There are at least two instances in which previous inoculation of a toxin derived from the agent concerned in the disease seems to give rise to definite protection by producing an active antitoxin immunity These instances are in diphtheria and in scarlet fever The first is apparently on a rather secure preventive basis and the second somewhat less fully proven

Antigen Therapy

It was discovered by Pasteur that the repeated injection of the brain substance of rabid animals during the relatively long incubation period will prevent in a very high percentage of instances the usual evolution of disease The treatment of tuberculosis by tuberculin i another instance of an adjuvant method of therapy which still is regarded favorably by many ex

its failure of general acceptance, must be regarded as indicating protection against typhoid fever

An allergic test was proposed by Gay and Minaker as pointing out carriers (immunes?) of the meningococcus

Prevention and Therapy of the Infectious Diseases by the Use of Antigens and Antisera

The prevention or cure of various infectious diseases by so called specific means depends on the use either of the disease agent in some modified form (vaccines), or the toxins of such agents, or on the use of the antagonistic properties (antibodies) produced by hyperimmunization of animals with the antigen In other words it depends on employing one or more of the various methods of producing an active passive or mixed form of immunity as we have described them We are interested at this point not in describing in further detail the mechanism of producing these beneficial results but rather in attempting to evaluate the success that has been reached in preventing and treating various infections

Antigen Prophylaxis

The first and still the most completely successful instance of antigen prophylaxis is smallpox vaccination where a modified living virus is used to induce a local form of the disease In countries where vaccination is practiced twice in a lifetime, smallpox has practically ceased to exist the protection afforded by this procedure is as nearly absolute as anything in biology can be The terms vaccination ' and vaccines although referring strictly to smallpox were employed deliberately by Pasteur in a more generalized sense, when he was able to produce similar conditions of protection with the known and isolated bacterial agents of disease The use of an attenuated vaccine in chicken cholera and a preparation of the anthrax bacillus, modified by heating in the prevention of splenic fever in cattle remain among the most striking examples of preventive vaccine therapy In general it may be stated that, whenever a preparation of bacteria that is alive can be employed with safety, a stronger protection is insured but none the less, a very definite protection in some diseases may be produced by using killed bacteria Prophylactic vaccination usually is produced by subcutaneous inoculation but in recent years the possibility of immunization by the gastrointestinal route has been raised again through the work of Besredka and Calmette The infectious diseases in which the most definite results of specific prevention have been obtained are, in addition to the two diseases mentioned chicken cholera and anthrax and

with or be the cause of a mobilization of proteolytic ferments Our own work on what we have already referred to as enhanced resistance shows that cell accumulations particularly of the mononuclear type produced by indifferent substances such as beef broth increase active resistance to even very virulent micro-organisms It is on this basis that we are inclined to explain certain forms of so-called antigen therapy as well as non specific protein therapy We do not deny that a specific antigenic protein may aid enormously particularly in prolonged infections by building up an active immunity as well

Antiserum Prophylaxis

The short duration of passive immunity conferred by the transfer of serum from hyperimmune animal or convalescent individual limits the usefulness of this type of protection It is only in those cases where exposure is great or infection is assumed to have taken place, that it is widely practiced The local administration of tetanus antitoxin after Fourth of July wound and in war injuries has proved highly effective The addition of combined antitoxins to the several organisms operative in gas gangrene has decreased still further the danger of infection Diphtheria antitoxin is employed routinely and wisely in families and asylums exposed to a declared case of the disease at least in those individuals with a positive Schick reaction In animal epidemics of hog cholera rinderpest and anthrax the corresponding antiserums are recommended

The serums of individuals convalescent from measles from varicella and from mumps have been employed as a preventive measure with distinctly favorable results (Park) although not employed on a wide scale owing to the difficulties in securing a supply and the relative harmlessness of the last two diseases cited

Antitoxin Therapy

The first proof of the practical usefulness of passive immunity which followed the discovery of diphtheria antitoxin still remains the outstanding example of a sovereign specific therapy Not only has the mortality from diphtheria been reduced from an average of 40% to from 7 to 14% but the incidence in a city such as New York per 100 000 of population fell between 1890 and 1910 from 134 to 14 5 This by no means fully expresses the usefulness of this remedy for it is found that in those cases treated on the first day the mortality is practically nil The antitoxin therapy against tetanus is by no means so good once the symptoms of the disease are manifest owing to the fatal anchoring on the brain stem of the toxin to be neutralized

perts. Some twenty years ago Wright suggested the employment of specific vaccines in nearly all recognized bacterial diseases and particularly in those that fail to respond to current methods of passive specific serum therapy. The conception of bringing into play "new areas of resistance" remains an important conception in the treatment of both localized and general infections although the detailed expectations of Wright have largely failed of confirmation. Vaccines are still used and usually indiscriminately when other methods fail but in only a few instances can they be recommended unhesitatingly. The most successful instances in which vaccines seem to be beneficial are in checking the spread of staphylococcus infections, in colon bacillus pyelitis and cystitis and in gonococcus arthritis.

Besredka in recent years has recommended an "antivirus" therapy in localized infections in which he employs a filtrate of the broth culture of the micro-organism concerned. This work in particular, as well as that of Wright, make us now inclined to explain the beneficial results which undoubtedly occur in vaccine treatment, as due to protein stimulation rather than to specific antigen action.

An extensive and growing series of protein substances are used not simply in testing for the allergic conditions manifested in hay fever, asthma and food susceptibilities but apparently very effectively in desensitizing or restoring to normal such hypersensitive individuals.

Non Specific Protein Therapy

The type of therapy by antigens just discussed has been supposed to owe its successes to the production of an active immunity against the specific infection concerned. It is probable that at least some of the beneficial effects noted, however, are due to another non specific factor that previously had been chanced upon in other lines of investigation. A number of instances of apparently successful therapy that have no specific relation to the etiological agent concerned have been noted in the infectious diseases but are dependent on the fact simply that a foreign protein has been employed. In spite of the interpretations that have been given for the effectiveness of "pyocanase" (Emmerich and Loew) "plasmine" (Buchner) and leucocytic extract (Hiss and Zinsser) it seems to us now self evident that whatever good they did might have been obtained by any other foreign protein substance. It has been shown that certain general infections like typhoid fever and arthritis may be markedly benefited or even aborted following the intravenous injection of any protein whether albumose, milk or typhoid vaccine. These benefits are associated with and we believe caused by an increase or mobilization of the leucocytes; this mobilization may be associated also

the hog cholera virus the rinderpest virus and the gonococcus No antiserums against streptococcus can be claimed to be effective other than in those instances such as scarlet fever, where the micro-organisms are dangerous through their toxins

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but even here the mortality has been decreased, particularly since intrathecal injections have been employed

There seems no longer reason to doubt that an antitoxin against the poison of the streptococcus concerned in scarlet fever has great value in checking the severer toxic manifestations of the disease A similar antitoxin to the closely related organism present in erysipelas although not so extensively tried appears valuable There is reason to believe that antitoxins to the Shiga dysentery bacillus and to the cholera vibrio are valuable in combating the corresponding infections An antitoxin to the several organisms concerned in gas gangrene, Cl edematis maligni, Cl Welchii and Cl edematiens has been used with apparent success Antitoxins to the three varieties of Clostridium botulinum have been prepared and are effective experimentally, but have never been employed therapeutically to any considerable extent Snake venoms vary individually in their poisonous components, but mortality from snake bite is distinctly lowered by employment of the corresponding antivenom (Do Amaral)

Antibacterial Therapy

The results following the extensive use by passive transfer of antiserums acting on bacteria rather than their toxins have been most discouraging We have already given our reasons for believing that their failure is due, not to the ineffectiveness of the serum itself, but rather to lack of the essential phagocytic cells, which presumably are present or quickly mobilized in sufficient numbers in the actively immunized animal The antiserum to the meningococcus alone has approached expectations, but has become effective only when introduced in the area where the infection is active (intrathecally) and where also phagocytic cells are abundantly present The mortality since the use of this serum has fallen from 60–80% to 20–30% and to a fraction of the latter figure when given early The finally accepted effectiveness of this serum has been delayed by failure to recognize at first the necessity for inclusion in the serum of antibodies active against the particularly predominating type of meningococcus present in the treated case A similar appreciation of the existence of types in other pathogenic micro-organisms, e g, pneumococcus is fundamental to any effective serum therapy

Antiserum has been used extensively in the treatment of pneumonia and with increasingly persuasive results It has not approached as yet in effectiveness the antimeningococcus serum and varies markedly in accordance with the type organism concerned Here again progress has been entirely concerned with perfecting and concentrating the antiserum rather than in consideration of the cell participation of the recipient Other antibacterial serums that are on a promising basis are those directed against anthrax, the plague bacillus,

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CHAPTER V

THE CHEMISTRY OF PROTEINS IN RELATION TO DISEASE

By WILLIAM T SALTER

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I

THE CHEMICAL NATURE OF PROTEINS

Proteins belong to the class of substances called colloids by Graham (1861) because like glue they form viscous solutions which cannot diffuse through parchment collodion or animal membranes Many of them form opalescent solutions Although not included in the category of crystalloids, many of them form crystals after appropriate laboratory treatment indeed Hartig (1850) demonstrated crystalline protein structures in seeds and nuts Nearly all of them are digestible by digestive enzymes They bind either acid or base according to the acidity of the medium

The Composition and Structure of Simple Proteins

The elementary compositions of different proteins are so nearly alike that the albuminous material in animal and vegetable protoplasm was once considered to be one substance in many protean forms (Mulder 1849) In 1842 however Dumas (Dumas and Cahours 1842) successfully demonstrated differences in the elementary composition of proteins but these were so small as to have little bearing on the behavior of these various substances Carbon phosphorus oxygen hydrogen and nitrogen were found to contribute fairly constant proportions of the molecule Sulphur and phosphorus were found in smaller and rather variable proportions Thus the sulphur content of insulin is over three per cent as compared with the nearly complete absence of sulphur in the milk protein casein So uniform however, is this average composition for many animal and vegetable proteins that for certain purposes of nutrition

the composition may be considered invariable. For nitrogen in particular a value of 16 per cent usually is sufficiently accurate, so that protein nitrogen figures may be multiplied by the factor 6.25 to convert them into the corresponding weight of total protein. More accurate and detailed analyses have been accumulated by the school of Osborne and Mendel (Osborne 1909), and show this assumption to be only approximate.

The typical composition of a protein is given by Hammarsten (1926) as follows:

C	50.5 — 54.6	per cent
H	6.5 — 7.3	"
N	15.0 — 17.6	"
S	0.5 — 2.2	"
O	21.5 — 23.5	"

The Constituent Amino-acids of Proteins

The clear differentiation of proteins on the basis of composition was a direct consequence of the isolation and description of the various amino-acids from which proteins are built. Leucine and glycine were isolated from proteins in 1819 and 1820 by Proust (1819) and Braconnot (1820). In the course of the following century the number of these known unit components has increased to nearly three score. The manner in which these amino-acids were combined in the protein molecule puzzled chemists for many years. Kossel (1896-7) forecast toward the end of the last century the polypeptide nature of the protein molecule and Hofmeister (1902) accumulated convincing evidence that the union of amino acids was an essential feature of its molecular architecture. Nevertheless our present conception of protein structure is based chiefly upon

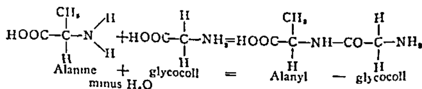


Fig. 1. Coupling of the amino acids alanine and glycocoll to form the dipeptide alanyl glycocoll.

the brilliant synthetic work of Emil Fischer. That eminent chemist demonstrated that, when two simple amino acids combine with each other to form a dipeptide, one free amino and one free carboxyl group remain, as illustrated by the diagram shown in Fig. 1. These in turn may combine with other amino acids to form polypeptides, as illustrated by Fig. 2. It will be observed that the peptide chain consists in a uniform repeating pattern of — NHCO — links

but that a multiplicity of substituted chemical radicles offers opportunity for great variety of structure

Emil Fischer (1906) pointed out the striking similarity of artificial polypeptides to peptones especially as regards their behavior with pancreatic juice This line of endeavor has been extended further by the enzymic synthesis of artificial proteins named plasteins by Wastenevs and Borsook (1930) Indeed Taylor (1909) prepared from amino-acids an artificial protamine which closely resembled the natural protamine and recently Salter and Pearson (1936) have described an artificial thyroid plastein which closely resembles thyroglobulin in its physico-chemical properties and biological effects

The work of Osborne Dakin and Abderhalden has demonstrated that on drastic hydrolysis with acid or enzymes the various natural proteins break down into sundry characteristic assortments of the two score amino-acids now known Analytical procedures for the quantitative analysis of amino-acids have improved continuously so that in some proteins nearly all the nitrogen has been accounted for Thus the analyses of ox muscle made by Osborne and Jones (1910) yield nearly 103 per cent of the value of the original ox protein This value of course includes the water added by hydrolysis of the peptide linkages, so that the theoretical total should be about 115 per cent

Of the two dozen amino-acids known one fourth are simple derivatives of aliphatic organic fatty acids Most of the others contain groups which are unique in the protein molecule and contribute to the characteristic behavior and metabolism of protein Among these may be mentioned cystine which contains sulphur, tryptophane which contains the indole ring tyrosine which contains a phenolic benzene ring and proline which contains the pyrrolidine ring

When analyses are made and tabulated of the commonly known animal and vegetable proteins a considerable variation is observed in the proportions contributed by each amino-acid Table I gives the composition in so far as it is known of several proteins as tabulated by Cohn (1931 p 870) It will be observed that in some proteins certain amino-acids are lacking or present in only small amounts As examples may be cited the deficiency of tyrosine in gelatin and the low cystine in casein

Not only may the substituted radicles in the protein contributed by each amino acid vary but the amino-acids themselves may be modified also by the formation of chemical derivatives Osborne for example concluded that glutamic and aspartic acids may exist in the protein molecule in the form of their amides so that in reality the actual building stones are respectively glutamin and asparagin

Further substantiation of the structure of protein molecules has been afforded by studies of the action of proteolytic enzymes The course of protein

the composition may be considered invariable For nitrogen in particular a value of 16 per cent usually is sufficiently accurate, so that protein nitrogen figures may be multiplied by the factor 6.25 to convert them into the corresponding weight of total protein More accurate and detailed analyses have been accumulated by the school of Osborne and Mendel (Osborne, 1909), and show this assumption to be only approximate

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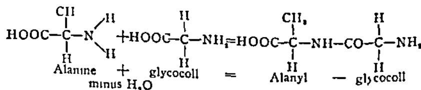


Fig 1 Coupling of the amino-acids alanine and glycocoll to form the dipeptide alanyl glycocoll

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digestion has been studied in vitro by many investigators Most recent and complete are those of Wilstatter and Waldschmidt Leitz and his school who have pointed out the high degree of specificity in their action Thus, certain enzymes found in the intestinal tract will hydrolyze only dipeptides containing a terminal carboxyl group and this fact can be used as evidence that the product of the tryptic digestion of protein contains such substances Other enzymes are found to act upon short polypeptides only whereas digestion with Northrop s crystalline pepsin (1935) yields only very long chains known as peptones or albumoses

Wasteneys and Borsook (1930) have shown that the breakdown of protein and its synthesis occur simultaneously with the enzyme catalyzing the reaction in either direction The rate of either reaction depends upon several factors among them the concentrations of protein and of its split products the acidity the temperature and the salt concentration The extent of the final equilibrium between protein and end products is affected largely by concentration and temperature Removal of end products either protein or polypeptide allows the reaction to proceed further in the corresponding direction Northrop and Waldschmidt Leitz with their collaborators have studied carefully the rate of digestion chiefly as a means of measuring the concentration of active enzyme Waldschmidt Leitz (1931) has summarized some of the results and pointed out that in physiological environments a multiplicity of enzymes exist Thus ordinary trypsin contains several enzymes some adapted to longer polypeptides than others or to special groupings For example the amino-polypeptidase isolated from the intestinal mucosa by Waldschmidt Leitz and Balls (1930) is specific for a definite type of polypeptide Similarly the carboxypeptidase isolated in crystalline form by Anson (1935) is highly specific for chloracetyl l tyrosine and closely related compounds

In the course of hydrolysis certain peculiar secondary findings have been noted Among these are the change in color of the biuret reaction the appear ance of dialyzable elements giving the ninhydrin test and the finding by Van Slyke and Birchard (1913-4) that free ammonia appears to the extent of one half the lysine nitrogen

The progress of digestion may be followed as Northrop did it in the case of pure proteins by physical measurements like viscosity or by measuring free carboxyl or amino groups as in the Van Slyke or Sorensen methods respectively Perhaps the best guide to the extent of protein splitting is the determination of free amino-nitrogen in relation to total nitrogen For certain purposes how ever physical procedures like dialysis through membranes of suitable permeabil ity may suffice

If peptide linkage is the explanation of the long-chained protein and peptone molecules there should be evidence that carboxyl and amino groups are liberated

AMINO ACID CONTENT OF PROTEINS

After Cohn (1931 pp 8,0-1)

	Albumins					Prolamines		Fibroin	Animal Globulin		Vegetable Globulin		Histones		Protamines	
	Egg Albumin	Serum Albumin	Lactalbumin	Casein	Gelatin	Gliadin	Zein	Fibroin	Serum Globulin	Bence Jones Protein	Cocoanut Globulin	Edestin	Globin	Thymus Histone	Salmine	Sturine
			%			%	%	%	%	%	%		%	%	%	%
Glycine	0 0		0 37	0 45	25 50	0 0	0 0	0 50	3 52		T	3 80	4 9	0 50		
Alanine	2 22	2 68	2 5	1 85	8 0	2 00	9 79	25 00	22		4 11	3 60	0 56	3 46	1 80	
Serine		0 60	1 6	0 50	4	0 3	1 02	80			1 76	33			1 1	
Valine	2 30		3 3	7 01	0	3 34	1 88	—			3 57	+				
Leucine	10 71	20 00	19 4	9 70	7 10	6 62	25 00	2 5	18 70		5 96	9	29 04	11 80		
[illegible]							0 0									
Proline	3 56	04	4	8 70	9 5	13 2	9 04	00	2 76	2 73	5 54	4 0	34	46	00	
Oxyproline				0 1	14	—	0	—				2 00	1 04			
Phenylalanine	5 0	3 00	2 4	3 88	1 40	35	7 60	1 50	3 84	4 92	2 05	3 09	4 4	—	—	
Methionine	—	—	—	0 40	+	—	—	—	—	—	—	+	—			
Cystine	0 68	6 04	4 25	26	0 18	2 27	0 80		0 67	1 74	1 46	1 36				
Tryptophan	23	0 53	2 60	1 54	0	1	20	0	2 28	1 67	1 25	1 46	6	0		
Tyrosine	4 0	4 65	1 95	5 36	0 0	3 4	5 90	00	6 7	7 36	3 8	4 55	4 63			
Histidine	7	1 40	2 6	2 5	94	3 35	0 82	0 5	2 8	2 68	42	2 85	0 96	50		8 8
Arginine	4 9	4 90	1 47	3 8	8	3 4	8	1 5	3 90	4 67	5 9	15 76	5 42	15 50	87 40	53 46
Lysine	3 76	3 0	9 89	8 35	5 92	0 69	0 0	0 65	8 50	6 79	5 8	3 58	4 28	7 7		1 12
Aspartic acid	6 2	3 12	9 3	4 10	3 40	77	1 8		2 54	2 17	5 12	1 19	4 43			
Glutamic acid	3 7	1 52	1 89	1 77	5 80	43 66	31 30		2 20		19 07	19 16	73	3 66		
β Hydroxyglutamic acid			1 00	10 50	0 0	7 70	5				0	0 0				
Ammonia	1 34	29	31	1 61	0 40	5 22	3 64		1 75	1 85	57	2 27		66		
Total	61 8	66 05	02 09	93 47	93 56	98 96	1 3 11	86 40	62 38	36 56	78 78	99 00	75 47	50 54	0 5	63 4

The Classification of Proteins

Two classifications of proteins have been proposed one by the English Society of Physiologists and the other by the American Society of Biochemists The two classifications are similar in that they describe three groups of compound

1 Simple Proteins
2 Compound or conjugated proteins
3 Derived proteins

In the first group are included

Albumins — Simple proteins coagulable by heat soluble in water and in moderately concentrated salt solutions Egg and serum albumins are typical examples

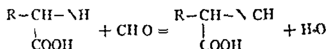
Globulins — Simple proteins heat-coagulable insoluble in water but soluble in dilute solutions of the salts of strong bases and acids These proteins like serum globulin characteristically are precipitated from less concentrated solutions of electrolytes than are albumins

Protamines and Histones — Simple proteins strongly basic not coagulated by heat soluble in ammonia and yielding large amounts of diamino-acids on decomposition The protamines are found in the ripe sperm of fishes They form insoluble salts with proteins e g with insulin Salmine from salmon sperm is typical

Other substances included in this group are the glutelins prolamines or gliadins These are found chiefly in plants They have relatively few dissociable groups which bind acid or base The English classification also includes phosphoproteins like caseinogen which the American nomenclature places among the conjugated proteins These phosphoproteins contain phosphoric acid coupled to the albuminous peptide chain in ester linkage P A Levene and Schormuller (1934) have found in phosphoserine an ester of phosphoric acid with the hydroxyl group in the amino-acid serine which indicates the sort of linkage involved in this class of protein

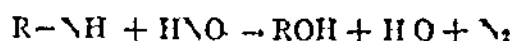
The second group includes certain proteins usually those associated with special function which are distinguished by being the bearers of special chemical nuclei or groups Such a protein is known as a conjugated protein and the special grouping was named by Kossel (19 8) the prosthetic group In such compounds the peculiar grouping usually is of a specific character not related to amino acids To it is attached the non specific protein chain which gives the molecule its colloidal size and modifies slightly the behavior of the peculiar prosthetic group Probably the best known example is the heme group carried by the protein chain in hemoglobin Bertin Sans and Moitessier (1893) first synthesized this protein artificially by conjugating globin with the hematin

in equal numbers when enzymic hydrolysis occurs That this is indeed nearly the case could be demonstrated by the techniques elaborated by Sorensen (1908) and by Van Slyke (1909–10) Sorensen titrated the newly released acidic groups with alkali using suitable indicators In order to do away with the neutralizing effect of the amino groups simultaneously released he took advantage of a reaction with formaldehyde studied earlier by Schiff (1901)



By this means the basic effect of the amino groups could be blocked

Van Slyke on the other hand measured the newly liberated $-NH_2$ groups by means of their reaction with nitrous acid to form nitrogen gas, as follows



In making such measurements one must take account of the fact that monoamino-dicarboxylic amino-acids, like glutamic acid, already have a free COOH group even when combined in the protein molecule Similarly di amino-monocarboxylic acids, like lysine have a free amino group even when centrally located in a peptide chain In general however, the number of mono-amino mono carboxylic acids predominates, and these yield no free acidic or basic groups when combined in protein A typical fragment of a polypeptide chain has been pictured by Cohn (1925) as shown in Fig 2

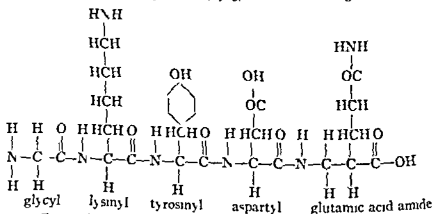


FIG 2 An hypothetical polypeptide After Cohn (1925 p 361)

The differences between the various known proteins then are to be ascribed to the assortment of the fundamental building stones of which each is composed. It is evident that the number of each type of amino-acid present and the order in which they are conjoined affords ample opportunity of protean variety in proteins

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nucleus More recently Hans Fischer and Zeile (1929 and 1933) have synthesized the hematin starting with simple laboratory materials Such investigation has confirmed the concept of conjugated proteins as the conveyors of groups having specific physiological function Other examples of such groups are the thyroxine in thyroglobin the specific carbohydrate fraction of pneumococcus antibody and the active groups in enzymes to be discussed in a subsequent section

Among the conjugated proteins are included

Chromoproteins — In these the prosthetic group is colored It may be hematin as in hemoglobin or the copper-containing nucleus of hemocyanin, the blue pigment in the blood of crabs and snails

Glucoproteins — The prosthetic group contains a carbohydrate radicle In mucin and cartilage it is mucoitin sulphuric acid or chondroitin sulphuric acid, respectively

Nucleoproteins — These are found in the chromatin of the nuclei of cells The prosthetic group is nucleic acid

In addition there is a third group of substances, known as derived proteins Among these substances the most important are those named 'primary protein derivatives in the American classification and ' hydrolyzed proteins" in the English classification This group comprises coagulated proteins and proteins altered by acids alkalies or by the action of proteolytic enzymes The hydrolytic end products of digestion viz proteoses, peptones and polypeptides are included

a *Proteoses* are soluble in water are not coagulable by heat and are precipitated by saturating their solutions with ammonium sulfate They penetrate membranes but slowly They give the biuret reaction These are the initial cleavage products in peptic digestion

b *Peptones* are soluble in water are not coagulated by heat and are not precipitated from saturated ammonium sulphate solution They are generally diffusible and give the biuret reaction

c *Peptides* are combinations of amino-acids united through the amino and carboxyl groups Many are synthetic They may or may not give the biuret reaction They are not heat coagulable They are named di tri , tetra , peptides etc according as they contain two or several amino-acids in the molecule

THE GENERAL CHEMICAL REACTIONS OF PROTEIN

The chemical reactions characteristic of protein may be arbitrarily divided into two groups (1) those due to the fundamental nature of the whole protein molecule and (2) those dependent upon the specific properties of the constituent amino acids Of course either constituent secondarily affects the properties of the other

In the first group fall the properties of splitting by proteolytic enzymes and the phenomena of amphoteric dissociation Closely allied are physical and physicochemical properties characteristic of proteins Thus proteins may be precipitated by the salts of heavy metals They also form insoluble compounds with many acids among which are tannic picric and phosphotungstic acid Most characteristic is the biuret reaction given by all native proteins and by many derived products When an alkaline solution of protein is treated with dilute cupric sulphate solution a violet tinge develops Schiff (1896) showed that the biuret reaction is given by a repeating pattern of carbonyl and amino groups In peptides the reaction is due to a general grouping of the following sort $NH_2 — CO — CO — NHR$ Pickering showed that cobalt salts gave an even more delicate reaction than copper salts

In the second group fall the specific reactions due to the peculiar substituted chemical radicles supplied by the various amino-acids The proteins show several useful color reactions which may be used to detect protein in solution and in body fluids or to test for presence of certain amino-acids For example Millon s reaction is given by tyrosine and consists in a red color obtained on heating with mercuric nitrate and nitrite Similarly the yellow xanthoproteic reaction with nitric acid depends upon the presence of phenylalanine and of tryptophane Tryptophane itself gives a number of bright color reactions among them the violet color with the glyoxylic acid reagent of Hopkins and Cole (1903) Many proteins contain in their molecule a carbohydrate nucleus which gives Molisch s color reaction with alpha naphthol The ninhydrin reaction is a very sensitive test for most amino-acids proteins and peptones A blue color develops on boiling with triketo-hydrindene hydrate Glycine gives this reaction in 1 10 000 solution but proline and urea which are not α amino-acids fail to react Other reactions are due to the presence of sulphur Black lead sulphide may be formed with lead acetate or a purple red color may be developed with sodium nitroprusside

Obviously no one of these reactions is absolutely specific for protein but a combination of several such positive tests gives important information both as regards its identity and as regards its composition

PRECIPITATION OF PROTEINS

Among the common methods of precipitating protein quantitatively from solutions containing the split products of protein Hiller and Van Slyke (1922) have reviewed and compared the following (1) colloidal iron and heat (2) tungstic acid (3) trichloracetic acid (4) ethyl alcohol (5) metaphosphoric acid (6) picric acid and (7) mercuric chloride The chief interest in the applicability of these reagents for analytical procedures centers about the

principle that in general the proteins are thrown out of solution with greater ease than are their split products Some precipitants fail to precipitate certain proteins whereas other reagents precipitate not only proteins but also higher albumose and even peptones On the other hand Hiller and Van Slyke found that tungstic acid and picric acid would nearly completely precipitate protein intermediate products like peptone, without precipitating amino-acids The final concentration of the precipitant used is also important For example Wasteneys and Borsook (1924–5) found that 2 percent trichloracetic acid would precipitate protein only whereas 10 per cent would precipitate albumose and peptone in addition In studies of protein digestion mixtures therefore the use of trichloracetic acid recommends itself The conditions of precipitation often are very important A certain time is required for complete precipitation of the protein fraction but if this be prolonged other fractions also are precipitated Likewise as shown by Merrill (1924) the pH value for acidity must sometimes be adjusted within rather close limits Peters and Van Slyke (1932 p 63) have discussed various methods for precipitating blood proteins in the preparation of protein free filtrates and for general purposes recommend trichloracetic acid or tungstic acid For tissue extracts heat coagulation may be preferred in special cases

The Quantitative Determination of Protein

Several recognized methods are available for determining the protein content of body fluids The protein may be coagulated and estimated by dry weight or by performing the Kjeldahl nitrogen determination Less reliable is the method of redissolving the precipitate and applying one of the protein color reactions In the case of plasma too the refractometric method of Reiss (1904) has been used but Guillaumin Wahl and Laurencin (1920) have shown that lipoids prove a serious complication and prevent its use where most often desired Moore and Van Slyke (1930) have used specific gravity also as an index of plasma protein

In determining the various fractions of plasma protein fractional precipitation at successive concentrations of salt is employed The protein content of one or more fraction is then determined Table II indicates the concentration of sodium sulphate at which precipitation of successive protein fractions is practically complete The scientific principle applied in this method is that illustrated by Fig 3, to be described later

The fractional separation obtained in a single operation is at best crude By convention protein in the filtrate from a single precipitation with half saturated ammonium sulphate saturated magnesium sulphate or 22 per cent sodium sulphate is calculated as albumin The latter two reagents are convenient if Kjeldahl

determinations are to be employed The method described by Howe (1923) for sodium sulphate is widely used Probably a sharper separation of these protein fractions can be made by Butler and Montgomery s (1932–33) application of phosphate buffers In separating fibrin from plasma Cullen and Van Slyke (1920) added calcium chloride to oxalated plasma in amounts sufficient to supply the optimum excess of dissolved calcium for the formation of a fibrin clot The protein of the fibrin clot so formed can be determined gravimetrically

TABLE II

CONCENTRATIONS OF SODIUM SULPHATE REQUIRED TO PRECIPITATE THE DIFFERENT PROTEINS OF BLOOD PLASMA

From Peters and Van Slyke (1932 p 680)

Protein	Na_2SO_4 Concentration	
	molar	*per cent*
Fibrinogen	0.76	10.6
Euglobulin	1.00	14.2
Pseudoglobulin I	1.25	17.7
Pseudoglobulin II	1.50	21.5

or by Kjeldahl s method For urinary total protein the most accurate methods are the gravimetric or Kjeldahl determination after precipitation with one of several reagents Among these precipitants are acid alcohol tungstic acid or Tsuchiya s alcoholic solution of phosphotungstic and hydrochloric acids (1908) For approximate routine clinical measurements Shevky and Stafford (1923) have developed a conveniently rapid method of determining the amount of precipitated protein by centrifuging it in special graduated tubes

PHYSICAL CHARACTERISTICS OF PROTEIN

As physical and chemical methods have been extended to clinical measurements the various properties peculiar to protein have lent themselves to adoption for clinical convenience For this reason the characteristic behavior and properties of colloids must be regarded as possible means by which to advance clinical methodology More important however is the fact that a sound interpretation of the behavior of proteins in disease rests upon a thorough knowledge of their inherent properties

The physical nature of proteins and their physical behavior can be resolved largely in terms of properties of the constituent amino-acids A fruitful method of investigation has been the use of x rays to determine the structure of amino-acid molecules X ray diffraction studies give the distance between carbon

and also explains why they are precipitated from biological fluids on dilution with water Similarly DeBye's "salting out" term is of the same form as that which describes the precipitation of proteins and amino-acids by electrolytes at various concentrations Accordingly, the salting out of pseudoglobulin and euglobulin from plasma meets with an explanation which may be compared with DeBye's treatment of the influence of ions on each other or on non electrolytes

In Fig 3 is shown the precipitating effect of salt for different proteins recalculated by Cohn (1925) It is clear that the solubility in each case is related to the concentration of salt present but that various proteins salt out' at different concentrations The mathematical description of each curve is given by the equation $\log S = \beta - K_S C$ where S represents the solubility of the protein and C the concentration of salt added to the solution The initial solubility before the large quantities of salt are added is represented by β K_s is the mathematical constant for the slope of the line It will be observed from Fig 3 that at half saturated $(NH_4)_2SO_4$, shown by the dotted line pseudoglobulin is nearly all precipitated whereas albumin remains largely dissolved The separation of globulin from albumin results from the application of this principle

Of course in general, larger molecules like euglobulin, tend to be squeezed out of solution earlier than smaller molecules like pseudoglobulin as the salt which is added e g ammonium sulphate attracts more and more water molecules to itself In addition it has been recognized since Hofmeister (1887-8) that salts in concentrated solution have specific effects or variations due to their peculiar individual composition The problem is further complicated by the fact that proteins like their component amino-acids have high dielectric capacity i e, a high capacity for absorbing electrostatic energy or charge

Of considerable interest physiologically is the viscous nature of protein solutions Here again the acidity of the medium and the electrolyte content of the solution are important factors When these are kept constant, as is often the case in biological systems the nature of the protein concerned and its concentration are important variables Within these limitations the viscosity of a solution is made up of the summated viscosities of the several protein fractions contained in the solution On this basis Cohn (1925) pointed the way for an analysis of the viscosity of blood and showed that its viscosity could be computed from the constituent protein fractions as shown in Table III

The viscosity η is expressed in its logarithmic form It will be observed that pseudoglobulin which comprises only one third of the total protein, yields nearly one half of the net viscosity Likewise the two globulins together, although comprising less than half of the total protein yield two-thirds of the net viscosity

At their isoelectric reactions the chief factor determining viscosity of proteins is their molecular shape. When the reaction of the solution is not isoelectric the electric charge upon the protein molecule affects viscosity markedly and this phenomenon becomes more important as the protein binds more acid or more base. This fact is particularly important because many proteins in nature like the serum proteins exist at acidities considerably removed from their isoelectric points at which points no excess of acid or base is bound.

The solubility of proteins too depends upon the dimensions and upon the charged condition of its molecules. The smaller proteins like egg albumin and

TABLE III

THE VISCOSITY OF SERUM CALCULATED FROM THE VISCOSITY OF SERUM PROTEINS

After Cohn (1925 p 420)

Protein	Per cent	log η
Serum albumin	3 84	0 088
Pseudoglobulin	2 37	0 101
Euglobulin	1 10	0 075
Total calculated	7 31	0 264
observed		0 236

serum albumin which contain the largest number of dissociable groups appear to be both crystalline and soluble. They have low viscosities are very soluble in water and are precipitated in crystalline form only from very concentrated salt solutions. Limulus hemocyanin and many plant globulins are only slightly soluble in water at their isoelectric points and may be crystallized at the isoelectric point by dialyzing and by concentrating their solutions. Their solubility under these conditions is increased by salt for which reason they are classified as globulins. The larger globulins of serum although they are soluble in salt solutions have not yet been crystallized neither have thyroglobulin nor casein the largest mammalian proteins whose molecular weights have been estimated been crystallized. These last proteins are very viscous and are precipitated by low concentrations of neutral salts. The routine separation of serum proteins with sodium sulphate or phosphate is based upon this relationship. At 22 per cent sodium sulphate at 37° C the bulk of the globulins have been precipitated whereas the albumin fraction remains dissolved.

In summary then the proteins that are small and of high valence seem to be readily crystallizable are soluble and of low viscosity whereas those that are large are very viscous are only slightly soluble when uncombined with acids or bases and have not yet been crystallized (Cohn (1925)).

Miscellaneous Properties of Protein Solutions

The surface tension of protein solutions is high, as evidenced by their tendency to froth or foam Du Nouy (1926) has made careful measurements of this property which is evident even in high dilution

Diffusion of protein molecules in solution through membranes is slow as reviewed by Northrop and Anson (19 9) This property is related to their large molecular size and accordingly the smaller molecules like albumin move faster than do larger molecules Closely related to diffusion is the permeability of amino acid and protein molecules through membranes As Hober (1936) has pointed out large proteins may be able to squeeze through the fine pores of membranes only with difficulty

Protein solutions too show characteristic optical effects Protein molecules are so large in comparison with other molecules that light rays entering a protein solution are more readily scattered This is the so called Tyndall phenomenon which is very marked in solutions of protein Many proteins show peculiar refractive effects with polarized light Thus Von Muralt and Edsall (1930) demonstrated that the molecules involved in muscular contraction when stirred mechanically in solution showed double refraction when examined under the polarizing microscope Von Muralt has applied this phenomenon to the study of muscle contracting in situ (1934)

The Amphoteric Nature of Proteins

W B Hardy (1899) described the migration of proteins in solutions carrying an electric current and interpreted the phenomenon as due to a real electrolyte dissociation at the surface of the particles In sufficiently acid solutions the molecules were found to migrate toward one electrode whereas in sufficiently alkaline solutions they migrated in the opposite direction They can be regarded as anions or cations of exceptionally high valence The net electric charge on such an anion presumably depends upon the number of free carboxyl groups and perhaps also upon certain hydroxyl groups The net charge of cations depends upon the histidine arginine and lysine residues in the peptide or protein molecule

Until recently these molecules were supposed to be undissociated, that is uncharged at the neutral or isoelectric point as indicated by their failure to migrate in an electric field The addition of acid or of alkali to such a solution or suspension of protein was presumed to form acidic or basic salts which dissociated into multiple ions of which one was the protein itself In recent years, however it has become more and more certain that proteins like amino-acids exist as hermaphroditic zwitter ions such that at the isoelectric point

the number of negative charges equals the number of positively charged groups Thus physical chemists have come to differentiate between the isoelectric and isoionic states (Cohn 1925) and to distinguish in addition a state of maximum charge These differences may be summarized as follows In the isoionic state the number of positively charged groups equals the corresponding zwitter ionic negative groups Due to their unequal distribution however, some groups may be more effective than others, so that the isoelectric reaction may not be precisely the same as the isoionic In addition there are other groups which dissociate only at pronounced acidity or marked alkalinity Such groups *determine the maximal amount of acid or base which can be bound* *In certain* proteins such as lactalbumin and casein in milk acid groups are in excess in others such as gelatin and edestin the number of basic groups in the molecule predominates

Analytical data indicates that in egg albumin and serum albumin the numbers of free acidic and free basic groups are nearly equal By contrast casein has half again as many basic as carboxyl groups Among proteins pepsin is perhaps the most acid due to its large excess of free carboxyl groups Preeminent among basic molecules are the smaller protamines which contain a large proportion of the basic amino-acid arginine To this fact is due their interesting property of combining with proteins like insulin having less alkaline isoelectric points

It will be observed from Fig 2 shown previously that even after peptide linkage has been formed between many amino and carboxyl groups there still exist free acid or basic groups These free basic or acidic groups are contained in the free chemical radicles projecting from the peptide chain They may combine in salt formation with acids or bases or with each other In addition it has been suggested that ring like structures known as diketopiperazines may be formed between different coils in the long protein chain which in many proteins assumes a roughly spherical form Recently Waldschmidt Leitz and Gartner (1936) however have expressed doubt that these rings occur naturally Certain proteins are known for the high percentage composition contributed by certain types of amino acids Thus the protamines contain high percentages of arginine and histidine which are rather basic amino-acids Acidic proteins are rich in the dicarboxylic acids aspartic glutamic and β hydroxy glutamic acids Thus the properties of the whole protein are based in large part upon the properties of its constituents The carboxyl groups and amino groups involved in the peptide coupling are of course unable to bind acid or base It is to the free carboxyl or free amino groups that the acidic or basic properties are chiefly due Studies have been made of the titration curves of many proteins of which that for serum albumin is reproduced here The amphoteric nature of the albumin is clearly demonstrated in Fig 4 by its ability to combine

either with hydrochloric acid or with sodium hydroxide according to reaction of the solution Note that at its isoelectric reaction near pH = 4 7, the protein is combined with neither acid nor alkali Many individual free or zwitter ionic

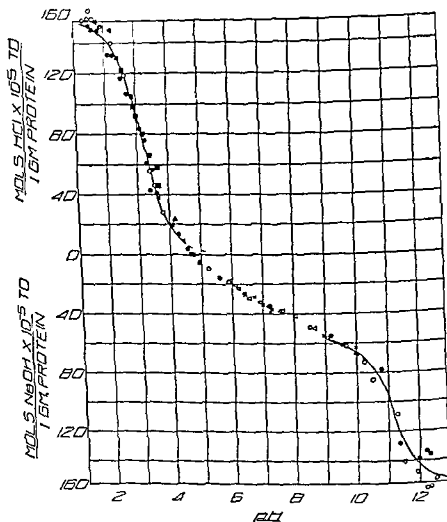


Fig 4 The binding of acid or of base by albumin with varying acidity From Cohn (1925 p 380)

groups are involved about 140 in the case of the serum albumin molecule Nevertheless it is frequently possible to describe the behavior of one link of the titration curve by a simple dissociation constant as if it were a monobasic acid Thus, the successive zones delineated by the titration curve of serum albumin

as shown in Fig 4 represent the dissociation of several groups of characteristic amino-acids as discussed by Cohn (1925)

As better analytical data for the number and type of the constituent amino-acids in each protein have accumulated the number of free basic and free acidic groups as estimated from these analyses has proved to be a good guide to the amphoteric behavior of the whole protein Closely related to this behavior are colligative properties of great interest For example the sharp precipitation zone for serum globulin in contrast to the wide range of insolubility of edestin from hemp seed can be ascribed to the reactivity of the free acidic or basic groups at various acidities of the respective solutions The swelling of gelatin and the viscosity of its solution at varying pH values also can be explained in analogous fashion Finally the solvent effect of dilute alkali or dilute acid upon proteins is the net effect of the dissociation of the free groups supplied by the constituent amino-acids

II

THE PHYSIOLOGICAL IMPORTANCE OF PROTEINS

Semipermeable Membranes and the Storage and Fixation of Protein Molecules

By far the most important functions of protein in the body are attributable to their large molecular size Functionally this magnitude is useful in the living machine because it preserves the organization of cells and tissues the contents of which are enclosed by membranes Obviously an interchange of metabolic products must occur across cell and tissue boundaries in the form of smaller molecules like glucose and oxygen The membranes however remain relatively impermeable to the larger protein molecules and are spoken of as semi permeable membranes for this reason The term is at best approximate because capillary walls and glomerular tufts do permit the passage of protein in large amounts on occasion and probably constantly in small amounts Nevertheless the storage of protein and of glycogen within the cells is evidence of a rather efficient discrimination between large and small molecules

In the metabolism of body protein the initial or anabolic phase consists of the assimilation by cells of amino-acids derived from food proteins The small diffusible amino-acids enter cells as will be seen later and through the action of intracellular enzymes called proteases are synthesized into large protein molecules which cannot escape This storage of nitrogenous material is analogous to the storage of glucose as glycogen When protein is required elsewhere as in

either with hydrochloric acid or with sodium hydroxide according to reaction of the solution Note that at its isoelectric reaction, near pH = 4 7, the protein is combined with neither acid nor alkali Many individual free or zwitter ionic

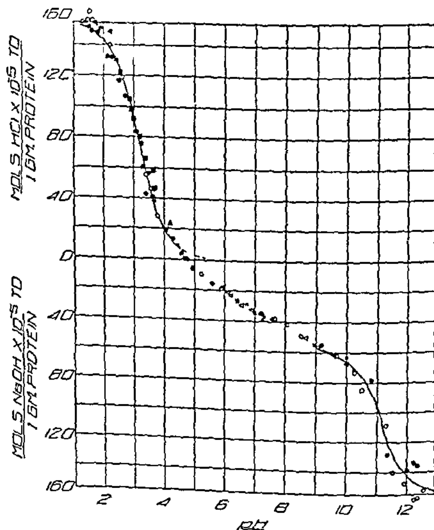


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Donnan's Equilibrium

The physical chemist Donnan pointed out (1924) that when a semipermeable membrane separates diffusible from non diffusible ions there will result an unequal distribution of diffusible ions like chloride on the two sides of the membrane. This law of Donnan's has been used to explain the fact that the chloride concentration in red blood corpuscles is only about half that of plasma and in muscle cells is less than one third that of plasma. Donnan's law theoretically relates the concentration of ions inside and outside of cells as follows

$$[Na^+]_{plasma} / [Na^+]_{cells} = [Cl^-]_{cells} / [Cl^-]_{plasma} = [HCO_3^-]_{cells} / [HCO_3^-]_{plasma}$$

Van Slyke, Wu and McLean have made such measurements as have Gilligan, Volk and Blumgart (1934). These are illustrated in Fig 14. Although the confirmation of Donnan's equilibrium is not absolutely quantitative, nevertheless it is obvious from such data that the phenomenon is important in determining the distribution of salts in the body.

The Rôle of Prosthetic Groups

To Kossel (1928) we owe the concept that many proteins contain specific chemical groupings upon which a highly specialized function of the body depends. Although he had in mind more especially the classical conjugated proteins it is now evident that the principle is of widespread importance. Our present immunologists conceive of protein antigens bearing specific groups. Indeed Landsteiner (1924) has produced new artificial antigens by diazotizing the serum proteins of the animal to be immunized. This altered protein behaves immunologically like a foreign antigen when injected back into the animal.

Likewise antibodies seem to consist chiefly of proteins bearing special chemical groups which may be detachable. Many of the hormones too are protein in character in their natural state. Thyroglobulin for example is known to be a protein of which thyroxine is but a constituent amino-acid. Salter and Lerman (1937) have presented evidence that the whole protein hormone may differ in its quantitative behavior from its constituent thyroxine.

In the case of blood pigments it is made clear from the work of Barcroft, Conant (1928) and others that, although the specific function of oxygen transport is subserved by one type of group, nevertheless this function is modified by the chemical state of a long albuminous peptide chain to which the prosthetic group is attached. Thus Bohr (1907) long ago showed that when base is removed from hemoglobin by the active tissues the molecule is able to hold less oxygen and forthwith gives up part of its oxygen store.

starvation or malnutrition this stored protein is autolyzed through enzymic action Thus the catabolic liberation of amino acids for distribution and utilization throughout the body is accomplished

How important the fixation of protein molecules is to special functions in the organism will be obvious from two well known examples When red blood cells are laked hemoglobinuria results, and free protein is rapidly excreted or destroyed Another specially localized protein is the enzyme which inverts cane sugar This sucrase is localized in the intestinal mucosa in consequence of which fact the sugar sucrose, when given intravenously is excreted quantitatively as a useless substance

The presence of smaller molecules within cells too is influenced by the larger molecules Van Slyke Wu and McLean (1923) found by quantitative analyses that the red cells of blood have the same concentration of total osmotically active ions as the serum when measured in terms of the electrolyte dissociated in a kilogram of water

This finding is consistent with the general truth that osmotic pressures are equalized through the organism The cells however contain a greater concentration of protein which by its bulk lowers the water content of the cells On the average the cells have per 100 c c volume only about 80 grams of water, in contrast to 92 per cent in the serum and 99 per cent in protein free transudates It follows that the unequal water distribution tends to make the concentration of the total electrolyte and total base less in cells than in serum This is an instance in which a property of proteins tends to decrease the total base in tissue cells

On the other hand the greater amount of base bound by cell protein tends to make the concentration of total base greater in the cells than in the serum As indicated in Fig 2 of Chapt VI of this volume by Peters this effect is overshadowed by the greater proportion of water outside of cells In short the electrolyte content of tissues is greatly influenced by the concentration of protein present Some properties of the protein tend to increase salt concentration other properties to decrease it

Bolam (1932) has presented evidence which indicates that on theoretical grounds the differential permeability of cell membranes may be due chiefly to the higher protein content of cells It is true that the major part of the potassium in the body exists in the cells whereas the sodium is found chiefly in the extracellular fluids It is also true that spinal fluid and serous exudates which are very poor in protein contain even less potassium than serum Moreover when tissues waste in disease or starvation the loss of cell protein is accompanied by loss of potassium These facts suggest strongly that retention of potassium within cells is somehow connected with retention of protein behind membranes

accumulate until about one half of all the peptide linkages have been hydrolyzed The remaining polypeptides require the catalytic effect of erepsin which is found in the mucous membrane of the intestine Interestingly enough a similar enzyme cathepsin is present in other tissues of the body

As yet the only enzyme whose active group has been isolated is the yellow respiratory enzyme of Warburg Richard Kuhn Rudy and Weygand (1936) recently have shown that lactoflavin combines with protein to form this enzyme The lactoflavin is particularly interesting because it is one of the substances formerly labelled vitamin B_2 and is intimately concerned with cell oxidation and with the health and growth of animals Kuhn has synthesized lactoflavin in the laboratory and shown that it is a complex pyrimidine derivative combined with a pentose (carbohydrate) chain

This work of Kuhn s amplifies and confirms that of Theorell (1935) who showed that vitamin B_2 plus phosphoric acid plus protein yield yellow enzyme reversibly When the protein is removed the yellow enzyme is no longer able to carry oxygen reversibly although it still is a potent vitamin and may supplement deficient diets When the protein is restored its properties as an oxidative enzyme return The relation thus established between a vitamin and an enzyme is highly illuminating from the standpoint of cellular physiology

In recent years Bergmann (1935) has shown in the case of dipeptidases that probably at least three different chemical groups must be appropriately located in the peptide in order to combine with the dipeptidase i e enzyme This geometric correlation amply confirms the lock and key concept of enzyme action long suspected The combination of enzyme with substrate then disintegrates into three pieces of which one the enzyme is free again to combine with another peptide

We are in short just beginning to understand how one protein may disintegrate another

Protein Solution as a Physiological Vehicle

The protein content of body fluids greatly modifies their properties The higher dielectric constants of such solutions (Cohn 1931) explains their ability to dissolve substances to a much greater extent than would a simple Locke s solution In the case of the blood the plasma proteins by their viscosity in solution greatly affect the dynamics of the circulation They probably also protect the circulating red cells against undue breakage In addition the amphoteric and osmotic properties of proteins help stabilize the acidity and salinity of the milieu interne

Bennhold (1932) has described in detail this vehicular function of the serum proteins He has pointed out that the transport of bilirubin of cholesterol and

Enzymes

The field of enzyme chemistry as yet is virtually unexplored from this standpoint. Nevertheless evidence is accumulating which points to the hypothesis that enzymes are, in general, conjugated proteins with specific active groupings. Indeed among the most important scientific advances of the past decade has been the clear demonstration that enzymes are protein in character. The crystallization by Sumner (1926) of the urease in the jack bean was the first significant step. The subsequent crystallization by Northrop of pepsin (1933) and chymotrypsin (Northrop and Kunitz, 1932) have added important evidence of the protein nature of enzymes.

It seems likely that the protein acts in a vehicular capacity in the sense that globin carries the heme grouping in hemoglobin. Northrop has shown moreover that the activity of the enzymes which he studied was almost completely lost when the protein was destroyed. Here again the enzyme behaves like hemoglobin, which loses its function as an oxygen conveyor when the globin is split up.

The percentage composition of crystalline pepsin was found by Northrop to be C, 52.4; H, 6.66; N, 15.4; S, 0.85; P, 0.078; Cl, 0.1; ash, 0.47. This obviously is the typical composition of protein material. Its activity is destroyed by heat, which of course coagulates many proteins. In the gastric cells the enzyme exists in the inactive form pepsinogen, which requires fairly strong acid to activate it at a pH value of at least 1.6. How the active pepsin differs from pepsinogen is not known.

In the case of the trypsin of chyme Northrop has shown also that the active material may be crystallized in protein form having the general composition C, 50.0; H, 7.20; N, 14.9; S, 1.10; P, 0; Cl, 2.88; ash, 1.2. Trypsin also exists at first in the pancreas as inactive trypsinogen. Curiously enough Northrop has shown his material to be activated not by enterokinase but by active trypsin itself. This sort of autocatalytic effect was wholly unexpected and its physiological significance still is obscure.

How enzymes act is only very imperfectly understood. It is clear that pepsin unites with the food proteins, because if these be strained off from the surrounding liquor the pepsin is removed. It is probable that this chemical union between pepsin and protein involves amino groups in the food molecule because, if a food protein be treated with formaldehyde, which blocks amino groups, pepsin will no longer digest it, although trypsin will. Enzymes which unite with the free amino groups of the proteins which they hydrolyze are called amino-proteases. Thus pepsin is an amino protease. Similarly trypsin is a carboxyl protease because it unites with carboxyl groups in the protein molecule. Free amino acids appear early in the course of tryptic digestion and

accumulate until about one half of all the peptide linkages have been hydrolyzed The remaining polypeptides require the catalytic effect of erepsin which is found in the mucous membrane of the intestine Interestingly enough a similar enzyme cathepsin is present in other tissues of the body

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Bennhold (1932) has described in detail this vehicular function of the serum proteins He has pointed out that the transport of bilirubin of cholesterol and

lipoids is intimately connected with serum proteins. He noted that injected dyes of different dispersion became equally diffusible in the presence of serum proteins. Furthermore, the electric charge on these particles was equalized and made uniform in the protein medium.

Because of these facts and because of their availability for chemical study the study of the proteins in body fluids has yielded much information of physiological and clinical value.

The Plasma Proteins

In blood plasma there are two types of protein, the globulins and the albumin. These are really mixtures, each of them, of different albuminous fractions which behave similarly. The two fractions are commonly separated on the basis of solubility. When salt is added to plasma, the globulins precipitate out first, and precipitation of them is complete when the salt concentration reaches a certain point, e.g., 22 grams of Na_2SO_4 per 100 c.c., or at saturation with NaCl or $MgSO_4$, or at half saturation with $(NH_4)_2SO_4$. This salting-out effect is illustrated in Fig. 3 previously described.

A special type of globulin is fibrinogen, which coagulates spontaneously in the presence of ionized calcium salts. In harmony with its great molecular size it may be precipitated in the presence of anticoagulants by very low salt concentrations. It accounts for less than 5 per cent. of the total protein as shown in Table IV.

TABLE IV

PLASMA PROTEIN CONTENT AND SPECIFIC GRAVITY IN NORMAL INDIVIDUALS
From Peters and Van Slyke (1931, p. 662)

Subjects	Values	Total Proteins	Albumin	Globulins including Fibrinogen	Alb./Glob. Ratio	Specific Gravity	Fibrinogen
Sixteen normal men	Average	7.00	4.44	2.58	1.72	1.027	0.3
	Highest	7.96	5.24	3.18	2.23	1.0254	0.2
	Lowest	6.53	3.95	1.96	1.43	1.0288	0.4
Sixteen normal women	Average	7.02	4.35	2.68	1.62		
	Highest	7.96	4.80	3.55	2.00		
	Lowest	6.34	3.77	2.18	1.38		

At somewhat higher salt concentration the euglobulin fraction is precipitated and subsequent additions of salt precipitate the pseudoglobulin Various investigators agree that the molecules of globulin are on the average considerably larger than those of albumin Such are the findings of Sorensen (19 4–5) and of Cohn Hendry and Prentiss (1925) Indeed Covaerts (19 7) places this discrepancy as high as four to one in human plasma The smaller size of albumin molecules is important first with reference to the ease with which they penetrate capillary walls and secondly with respect to their greater osmotic effect per gram of protein or protein nitrogen Normal values for various serum protein fractions are given in Table IV

Base Binding by Plasma Proteins

In the blood the plasma proteins exert a buffer action by virtue of their weakly acidic properties This effect however is of minor physiological significance More important is the amount of base bound Van Slyke, Hastings Hiller and Sendroy (1928) have determined that protein binds about 17 milli equivalents of base in blood Protein therefore succeeds Cl^- and HCO_3^- as the third most important acid in the blood plasma Especially important is the rôle which protein plays in binding blood calcium In fact McLean and Hastings (1935) have shown that the concentration of protein in plasma is an important factor in determining the concentration of ionized calcium in plasma The plasma calcium in mg per cent may be expressed mathematically as a function of the serum protein (Peters and Eiserson 1929)

Serum calcium mg per cent $= 0\ 556 \times$ protein grams per cent $+ 6$

It will be noted that protein constitutes the chief solid matter dissolved in plasma and for this reason is the chief determinant of plasma specific gravity which is close to that of sea water It is evident from Fig 5 that specific gravity may be conveniently used to determine both protein content and colloid osmotic pressure or oncotic pressure because these are nearly proportional to the protein content of plasma

Determination of Plasma Proteins

The nitrogen of protein in the plasma so far exceeds the non protein nitrogen i e urea uric acid etc that clinically protein is ordinarily calculated from the total nitrogen after wet ashing by some sort of Kjeldahl technique (Salvesen 19 6) Refractometric determinations by the method of Reiss (1904) unfortunately are often vitiated by high lipoid concentration Inasmuch as lipemia is common in disturbances characterized by protein deficit this latter method has at best a limited usefulness

Normal Variations in Plasma Protein

When the total amount of protein in the entire blood is changed the concentration of protein per unit volume is altered provided blood volume remains constant For instance Darrow and Cary (1934) found that premature

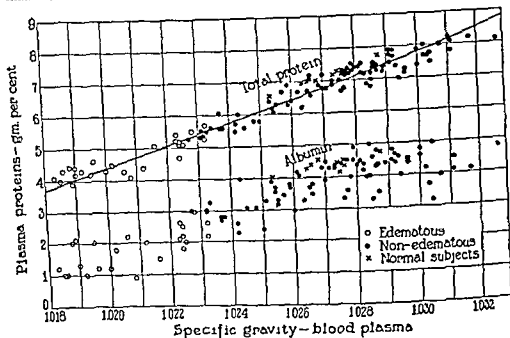


Fig 5 Relationship of protein content of plasma (heparin as anticoagulant) to specific gravity and edema in patients 118 observations on 75 patients with Bright's disease From Moore and Van Slyke (1930 p 342)

infants show a hypoproteinemia possibly based upon inadequate nutrition for blood building There is a gradual increase in the concentration of serum proteins during the first 18 months of life (Mello-Leitao, 1916) Diet too may influence plasma protein Frisch Mendel and Peters (1929) have demonstrated hypoproteinemia in rats maintained continuously on diets deficient in protein A similar effect was found by Bruckman D Esopo and Peters (1930) in patients suffering from protein starvation The deficit affects the albumin fraction chiefly In pregnancy there is a fall in serum protein during the first six months (Plass and Matthew, 19 6) which is due to the change in albumin concentration Subsequently a rise in fibrinogen occurs, and near term normal values for total protein are found (Oard and Peters 1929)

Likewise dilution or concentration of the blood may alter protein concentration Minor variations have been noted in excessive water drinking (Priest

ley 1916) and in abstinence from water (Keith 1924) Similarly vigorous exercise (Rowe 1915-6) heat and sweating may produce slight changes in normal individuals Local stasis may also result in concentration of venous blood Prolonged use of a tourniquet or even hanging the arm vertically for ten minutes (Yamaguchi 1926-7) may concentrate the blood through loss of water from the vessels Hyperglycemia may dilute the blood temporarily but if diuresis with glycosuria ensues dehydration and concomitant rise in protein concentration may follow (Keith 1924) On the whole these normal variations in plasma protein rarely are striking

Effect of Drugs on Plasma Protein

Diuretics probably produce an initial dilution of plasma protein followed by a concentration when diuresis ensues Hypertonic sodium chloride when injected or sodium bicarbonate when fed produce slight dilution of the plasma On the contrary acid producing salts (Gamble Blackfan and Hamilton 1925) concentrate the protein and so does urea when diuresis is produced

THE ONCOTIC PRESSURE OF PROTEIN IN RELATION TO WATER BALANCE

Although the proteins themselves exert a partial osmotic pressure of only 30 mm of mercury as against the 5000 or 6000 mm exerted by the crystalloids of plasma nevertheless this oncotic pressure plays a decisive role in the hydrodynamics of the circulation Starling (1895-6) first measured this partial pressure by dialyzing plasma against physiological saline He showed also that edema disappeared from the leg of a dog perfused with serum whereas perfusion with Ringer s solution failed to decrease edema The reason for this effect he pointed out is that crystalloids and water pass readily through vessel walls whereas colloidal protein molecules ordinarily are held back Inasmuch as the oncotic pressure is intermediate between arterial and venous blood pressures it aptly balances the mean capillary pressure In this manner an equilibrium is maintained between the hydrostatic pressure of the circulating blood and the oncotic pressure' of the plasma proteins Briefly stated the arteriolar pressure transmitted to the proximal end of the capillary squeezes fluid A out of the blood through the vessel wall Conversely at the distal end of the capillary fluid B is sucked from the tissue paces back through the membrane into the blood The balance involved is illustrated by Fig 6 after Christian (1936) From the diagram it is evident that theoretically a disturbed balance between the hydrostatic pressure and the oncotic pressure may result in transudation and the development of edema In a subsequent section it will be seen that a fairly satisfactory concept of edema may be formulated in these terms

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The Origin of Protein in Tissue Fluid and in Lymph

The simplified picture of water balance about a blood capillary thus evolved by Starling (1909) and elaborated by Schade (1927) cannot be accepted without certain reservations. Among these the chief complication is the indubitable permeability of blood capillaries to plasma protein. It is tempting to consider the capillary wall as a simple membrane, which withholds large particles

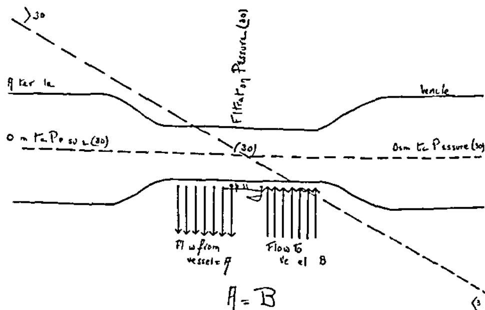


FIG 6 The normal balance between capillary hydrostatic pressure and plasma oncotic pressure. After Christian (1936)

but allows water, urea and dextrose to pass through easily. The blood capillary, however, is not so simple. Drinker and Field (1931) observed the passage from the blood into the lymph of graphite (1 μ in diameter), calcite (1–2 μ), pneumococci and even microfilariæ (40 μ long and 5 μ broad). Despite the large size of these bodies no injury to the blood capillary could be demonstrated. In short, the blood capillary is not a simple membrane. Lymph wherever collected invariably contains albumin, globulin and fibrinogen as evidence that a certain degree of permeability to protein exists in the normal capillary wall. This concentration of protein in the lymph is higher in the limbs of resting animals. White, Field and Drinker (1933) found however that during uniform activity the flow of lymph increases to a uniform rate and at this constant flow the protein varied from 0.5 to 1.5 per cent of protein. It is evident that the protein which has escaped into perivascular tissue spaces must hold water and

so retard the return of fluid into the circulation In the skin of frogs studied by Churchill Nakazawa and Drinker (1927) the colloid osmotic pressure of the lymph averaged 4 cm of water and in consequence reduced the average colloid osmotic pressure of the blood plasma from 7 1 to 7 1 minus 4 2 cm or 2 9 cm of water It is interesting however that this net oncotic pressure is lower than the actual hydrostatic pressure measured by Landis (1930) whereas the oncotic pressure itself uncomplicated would be too high to permit the ' squeezing out of water postulated by Starling In short fluid leaves the capillary partly by virtue of the protein which also escapes through the capillary wall Drinker (1927) showed furthermore that normal plasma protein possesses an unexplained property which in itself influences the permeability of capillary walls In this respect plasma differs from a solution of gum acacia having the same colloid osmotic pressure

Because of the extravascular protein which accumulates with edema an extravascular colloid osmotic pressure develops against which the return of fluid to the blood must be effected Fortunately the lymphatics usually are efficient in removing this protein although they do little to minimize the abnormal filtration of water They supplement the capillaries in maintaining water balance merely by keeping down the concentration of protein in the tissue fluid Peters (1935) has discussed this lymphatic circulation in detail Whether or not variable permeability of the capillary wall throughout its length as suggested by McMaster Hudack and Rous (1932) complicates the problem seriously, remains to be ascertained by further study

The Permeability of Capillaries to Protein

Haynes (1932 b) showed that egg albumen or hemoglobin when injected intravenously into the dog are soon found in the subcutaneous lymph It will be remembered that these proteins have molecular weights not far from that of serum albumin That native plasma proteins also pass freely through the capillaries has been demonstrated by several investigators Conklin (1930) employing an ingenious technique in frogs was able to infuse Ringer s solution at a slow rate and by this means to wash nearly all the protein out of the blood The protein of course escaped through the lymphatics Isayama (1924-5) likewise showed that the total blood volume of the frog entered the lymphatic system and returned 50 times a day Whether albumin escapes in greater proportion than globulin has not been decided; Saito and Nakazawa (1932) confirm Wells (1932) in finding the oncotic pressure per gram of protein the same in lymph as in blood Nevertheless there seems to be relatively more albumin in lymph as would be expected from its molecular size

Starling himself showed conclusively that there is a difference in the capil

lary permeability of different mammalian organs We know now that under normal conditions protein which has left the blood vessels or which has been placed, experimentally in the subcutaneous areas is unable to pass back through the capillary endothelium but must return to the blood stream by the lymphatic route After plasmapheresis however when the blood protein has been reduced to around 3 per cent, the blood volume is restored by withdrawal of fluid from the tissues Under these circumstances there no longer exists both a pressure and a diffusion gradient of protein in the outward direction from blood to tissues Accordingly foreign protein which has been infiltrated in the subcutaneous tissues together with water and salts, may, as Field and Drinker (1931 a) showed be taken up by the blood directly The capillary endothelium must therefore be regarded as permeable to protein in both directions even though with normal pressure and osmotic relations protein which has left the blood usually is returned by the lymphatic route alone Of course, the interstitial fluid of skin and fasciæ may also furnish a means of conveying subcutaneous protein off to distant lymphatics Moreover as Peters (1935) has pointed out many perplexing problems must be solved before the facts at hand can be harmonized with the fundamental principles of thermodynamics.

The Tissue Fluid

Drinker and Field (1931) believe that the tissue fluid possesses an approximate degree of identity with lymph The protein content will vary with changes from rest to activity and with conditions which alter the permeability of blood capillaries Accordingly, tissue fluid from the subcutaneous tissue spaces contains blood proteins in amounts varying roughly between 0 3 and 4 0 per cent the high values representing transient states Landis Jonas, Angevine and Erb (1932) conclude actually lymph represents tissue fluid after the absorption has been carried to as complete a stage as conditions in the blood stream permit Capillary lymph and tissue fluid are thus as it were a common reservoir to which the blood capillaries make additions of fluid or by reabsorption, withdraw it During rest protein leaves the blood capillaries and fills the tissue spaces and lymph capillaries Simultaneously reabsorption of water into the blood capillaries concentrates the protein which must be collected into the lymphatics The actual protein concentration at any moment is therefore, the net effect of a dynamic equilibrium

The Proteins of Tissue Fluid and of Lymph — When as Turner has showed venous obstruction causes rupture of capillaries gross leakage of plasma protein may occur In such instances the lymph protein rises to 3 or 4 per cent Ordinarily however the protein concentration in subcutaneous lymph varies with the degree of activity in the animal Heim (1933) has studied the

subcutaneous lymph in dogs and found its protein content to range from 1 4 to 4 6 per cent Drinker and Field (1933 Table 5) found it to be between 1 8 and 2 3 per cent in anesthetized animals lying prone It is important to note that these values were found in lymph obtained from cannulated lymph vessels an essential technical advantage In active animals however it was lower between 0 5 and 1 5 per cent In man it was found to be 0 69 per cent at rest as collected from a vessel over the internal malleolus but 0 49 per cent during walking Thoracic duct lymph from man dog and horse usually varies between 2 and 4 5 per cent although values have been obtained as high as blood plasma and in starvation below 1 per cent

Lymph contains fibrinogen and prothrombin Howell (1914) showed that it clots more slowly than does blood because of a lack of thromboplastic material which is associated with the blood platelets especially The lymph also contains enzymes Hamill (1906–7) found amylase and lipase in human chyle Osato (1920), in addition to diastase found lipase and protease in thoracic duct lymph

In general the albumin globulin ratio is higher than in blood because the smaller albumin molecules traverse the blood capillary walls more rapidly Morawitz (1906) found in the thoracic duct lymph of dogs 2 1 to 2 4 per cent globulin and 3 3 to 3 6 per cent albumin More recently Wells (1932) has studied the lacteal lymph of dogs and found about 1 3 per cent globulin and 1 7 per cent albumin Field and Drinker (1933 p 114) state that it is probable that in subcutaneous lymph the preponderance of albumin would be even higher

Field Leigh Heim and Drinker (1934–5) determined the total protein and the albumin and globulin fractions of lymph and serum simultaneously in dogs They found that the albumin globulin ratio was invariably higher than that of the corresponding serum The total content of the lymph was always lower than the serum protein but as Wells (1932) also has suggested for a given level of the serum protein concentration the protein content of the lymph may vary only within certain fairly definite limits Of course this is to be expected if lymph protein is merely serum protein which has leaked out of the blood capillaries The mean values found for total protein were as follows in cervical lymph 0 58 in leg lymph 0 30 in thoracic duct lymph 0 66 in liver lymph 0 84 per cent As might be anticipated from the Donnan equilibrium effect of protein the chlorides tend to be somewhat higher in lymph than in blood Likewise calcium is a trifle lower

As indicated in Table V the colloid osmotic pressure of lymph depends upon the protein content With the exception of liver lymph the osmotic pressure per gram of protein is close to 50 mm of water as is that of the serum For liver lymph the value obtained is 33 mm It is interesting that the effective

lary permeability of different mammalian organs We know now that under normal conditions protein which has left the blood vessels or which has been placed experimentally in the subcutaneous areas is unable to pass back through the capillary endothelium but must return to the blood stream by the lymphatic route After plasmapheresis, however when the blood protein has been reduced to around 3 per cent the blood volume is restored by withdrawal of fluid from the tissues Under these circumstances there no longer exists both a pressure and a diffusion gradient of protein in the outward direction from blood to tissues Accordingly foreign protein which has been infiltrated in the subcutaneous tissues together with water and salts may, as Field and Drinker (1931 a) showed be taken up by the blood directly The capillary endothelium must therefore be regarded as permeable to protein in both directions even though with normal pressure and osmotic relations protein which has left the blood usually is returned by the lymphatic route alone Of course, the interstitial fluid of skin and fasciæ may also furnish a means of conveying subcutaneous protein off to distant lymphatics Moreover as Peters (1935) has pointed out many perplexing problems must be solved before the facts at hand can be harmonized with the fundamental principles of thermodynamics

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the stomach serving merely as a reservoir which holds the protein until it is largely liquefied The albumoses and peptones ultimately are delivered into the intestine where they mix with the pancreatic juice Formerly it was stated simply that the trypsinogen in the pancreatic secretion was changed by the enterokinase of the succus entericus into active trypsin As outlined in a previous section however we now know that the activated pancreatic secretion contains a series of ferments which act on successively smaller fragments of the peptide chain Moreover these ferments overlap each other in the size of peptide which they affect This complicated series of enzymes then attacks the peptones and any undissolved or unsplit fragments of protein coming from the stomach The resulting digest contains chiefly short-chained peptides as London and Rabinowitch (1912) showed Finally either before or after entering the intestinal mucosa the digest products encounter a third hydrolytic enzyme erepsin which carries the hydrolysis of peptides still further toward complete separation into amino-acids The bulk of the protein originally ingested finally is absorbed into the blood stream in the form of amino-acids Nevertheless a certain small fraction possibly is assimilated in the peptide stage Abel (1919) indeed has isolated a peptide from the blood Moreover the peptide of thyroxine has been shown by Salter Lerman and Means (1933) to be absorbed efficiently whereas the single amino-acid thyroxine itself is not consistently assimilated

In recent years data have accumulated which suggest that at times intact protein may be absorbed The experiments of Prausnitz and Kustner (1921) on artificial local anaphylaxis to fishy food cited in a later section strongly indicate the assimilation of intact fish protein Likewise the observations of Alexander (1936) on egg albumin indicate that the thoracic duct may contain appreciable amounts of egg protein shortly after its ingestion Certain experiments with thyroglobulin highly effective by mouth suggest the same thing Although the amounts of protein so absorbed must be very small nevertheless in the field of allergy immunity and of endocrinology these small amounts may have a vital significance in the initiation or treatment of disease

The Absorption of Protein

Kugler (1918–9) gave to each of four small dogs 300 gm of meat and analyzed the contents of the stomach and small intestine for nitrogen at increasing intervals after feeding He found a very constant supply of protein to be present in the intestines 80 per cent of which was in the form of polypeptides or amino-acids The rate of absorption compared quite closely with the curve of urinary nitrogen elimination Within eight hours about 60 per cent of the protein had been absorbed and within twelve hours over 80 per cent

osmotic pressure for leg lymph, i e, the colloid osmotic pressure of the blood serum minus the colloid osmotic pressure of the lymph serum, was 14 8 mm of mercury This value of course, represents the net oncotic pressure against which fluid must be squeezed out from the capillary by the hydrostatic pressure

TABLE X

THE COLLOID OSMOTIC PRESSURE OF LYMPH
From Drinker and Field (1933 p 121)

Author	Kind of lymph	Protein Concentration	Average	Number of dogs	Osmotic Pressure	Average
		per cent			*cm of water*	
Loewen Field and Drinker (1931)	Cervical	1 68–3 38	2 23	7	14 2–19 5	16 6
	Thoracic duct	2 1 –4 93	3 62	7	13 8–34 4	24 4
Wells (1932)	Lacteal	1 67–4 55	2 97	13	5 7–21 4	12 5
Saito and Nakazawa (1932)	Thoracic duct	3 40– 53	4 88	20	11 0–28 0	17 2

*Refractometric determinations

of the circulating blood The figure is not far from the hydrostatic venous pressure of 14 mm of mercury as determined by Drinker and Field (1933 p 14-) in the leg of a normal dog In this connection Haynes (1932 a) has demonstrated that hemorrhage with resulting fall in arterial blood pressure decreases the flow of lymph and increases its protein content Conversely hyperemia due to venous obstruction produces the reverse effects

III

THE PHYSIOLOGICAL BASIS OF PROTEIN METABOLISM

DIGESTION AND ASSIMILATION

The past two decades have seen few striking alterations in our concepts of protein digestion As Spallanzani and Beaumont showed the proteins enter the stomach and are digested to the stage of albumoses and peptones These substances often are more soluble than the native protein and much more soluble than denatured or coagulated protein or tissue Their molecular weight, however, still is rather large roughly about 3 000 and from this fact it is clear that peptic digestion cleaves the protein molecule into relatively few fragments During normal digestion products are not absorbed from the stomach

nitrogen in muscles could not exceed 75 mg per cent, although the liver could take up much greater amounts Thus the tissues are in some sort of equilibrium with the blood so that a low concentration of amino-acid is preserved

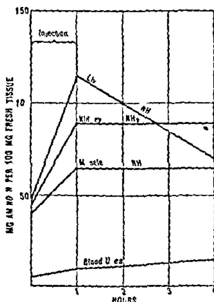


FIG 7 The absorption and retention by different tissues of amino-acid injected intravenously After Van Slyke and Meyer (1913 b)

in the circulating medium When the supply of amino-acids in blood is no longer renewed by food as in starvation amino-acids again move back into the blood from the tissues The free amino-acids in the tissues presumably are in transition about to be synthesized into cell protein or just recently released from disintegrating cell protein Unlike storage foods e g, glycogen the amino-acids do not disappear in starvation On the contrary they tend to increase slightly in the tissues of a fasting animal

Synthesis of Body Proteins

Provided that the proper assortment of amino-acid be present nitrogen equilibrium will be maintained or in growth increasing amounts of protein will be stored as discussed in a subsequent section on essential amino-acids If some of these are lacking less essential proteins are autolized to supply and maintain the protein structure of more essential organs If this state long continues a condition of malnutrition will occur as will be shown later

When protein in the food has been digested and absorbed the story of its further part in physiological processes resolves itself chiefly into the metabolism of its constituent amino acids They are the stuff of which body protein is synthesized and which is again liberated when tissue protein is catabolized Abel Rowntree and Turner (1913-4) obtained a filtrate from circulating blood by vividiffusion and from the blood filtrate isolated pure amino-acids The primary amino nitrogen of this fraction in human blood amounts to about 5 to 8 mg per cent Even after the ingestion of protein this value in man rarely increases more than 2 mg per cent, and prolonged fasting appears to effect little change Age sex and pregnancy likewise, are all without significant influence upon the level of amino acid nitrogen in the blood Nevertheless there is presumably a continual flow of these substances via the blood stream from the intestine to the liver and between other tissues

When amino acids are not being absorbed from the intestine they must be obtained by constant autolysis of body protein Conversely, when amino-acids are absorbed and stored tissue protein may again be synthesized After the feeding of protein the amino acid content of the blood increases in dogs and in men Delaunay (1910) found 3 3 mg per cent of amino nitrogen in the arterial blood of a fasting animal but 6 8 mg per cent after a meal and 11 1 mg per cent in the portal blood Van Slyke Cullen and McLean (1915) showed also that simultaneously with the fall in amino nitrogen as blood passed through the liver, there was a corresponding increase in urea nitrogen In men Folin and Berglund (1922) found increases ranging from 0 to 2 mg per cent in the venous blood after protein meals In evaluating these figures it should be remembered that nitrogen constitutes only a small part of the weight of an amino acid and that the actual percentage of whole amino acid in blood is about one fifth to one half that of glucose

Storage and Mobilization of Protein

Soon after entering the circulation amino acids disappear from it again Van Slyke and Meyer (1913 a) injected twelve grams of alanine into the vein of a dog and found that five minutes later 90 per cent of the material had left the circulating blood After the ingestion of protein a similar removal of the absorbed amino-acids occurs Van Slyke and Meyer showed that this first removal of amino acid was due chiefly to simple physical absorption in the tissues and tissue fluids In Fig 7 are shown this absorption and retention by different tissues of amino-acid injected intravenously

The amino nitrogen in tissues is five to ten times as concentrated as in blood Indeed the amino-acids usually constitute 2 to 4 per cent of the dry weight of the various tissues Van Slyke and Meyer (1913 b) found in dogs that amino

Protein Catabolism

Nitrogen Elimination after Protein Ingestion

Protein may of course be hydrolized and burned for energy Most of the protein nitrogen in the daily diet is excreted as urea and Levene and Kober (1909) found that when single amino-acids were fed to dogs they were excreted entirely as urea In similar observations on man Haas (1908) found that the curve of nitrogen elimination after a meal of mixed foods showed two maxima one in the second hour, the other in the fifth The first was presumably due to the early absorption of liquids taken with the meal the net result of which was to remove nitrogenous end products already in the system The second rise corresponded to the absorption of food protein A preliminary diuresis curtailed the primary rise Evidently for short periods nitrogen excretion is not a true index of urea production The results of von Wendt (1905) in man indicate that sulphur is eliminated more rapidly than the nitrogen of protein On the other hand phosphate appears more slowly

This process of amino-acid catabolism is insolubly connected with the liver and with the formation of urea In the normal animal Levene found that practically all of the amino-acid nitrogen not retained in the body was excreted in the form of urea or of ammonia derived from it Protein food to be sure yields acid products which must in part be neutralized in the kidney by ammonia and this ammonia nitrogen comes from the amino-acids Nevertheless the amino nitrogen probably is first turned into urea in the liver and then back into ammonia in the kidneys a possible intermediary being arginine (Krebs and Henseleit 1932)

Van Slyke Cullen and McLean (1915) found that early in the absorption of a protein meal the liver begins to transform into urea the first amino acids that reach it via the portal vein This was true even in the previously fasted animal Van Slyke with Cullen (1917) also found that during the ingestion of meat by dogs the urea content of the blood increased about mg per cent in passing through the liver The fact that amino-acid nitrogen showed the reverse change indicated this material as the source of urea in protein breakdown Similar results were found by Witts (1929) who studied in man the effects of the ingestion of 25 gm of glycine upon the blood amino nitrogen and the blood urea As appears in Fig 8 the amino nitrogen in the blood of men after such a meal rises 2 to 6 mg per cent to attain a peak in about two hours Meantime there is a slower increase in urea formation which reaches its high level somewhat later

It now seems probable that the liver is the chief site of urea formation in man Jansen (1915) has confirmed the older observations that when isolated

The Origin and Concentration of Body Proteins

In fresh muscle and liver tissue protein contributes a little over 20 per cent of the gross net weight The analogous figure for heart is 16 per cent, for kidney 17 per cent and for brain 10 per cent By way of contrast it will be recalled that raw egg white contains 12 per cent of protein milk over 3 per cent and whole raw oysters about 6 per cent How the protein originates in animal tissues is still an obscure problem Our most suggestive information arises from studies of autolysis in which the breakdown of protein has been studied It seems likely that the enzymes concerned with the splitting of protein also catalyze its synthesis, when split products accumulate in high concentration The synthesis of protein may thus be conceived of as a mass reversal of autolysis catalyzed by the tissue enzyme cathepsin, or related proteases

Many years ago Abderhalden (1916) was able to demonstrate that in this way new protein like material could arise in digests of various tissue proteins including that of the thyroid He showed also that the proteases of each tissue were specific for autolysates of that particular organ Thus, in a crude way he explained not merely how protein might originate but also why each organ built up a protein peculiar to itself

The new protein is formed of course from the amino-acids of the blood This fact has been clearly demonstrated by Cary (1920) for the production of casein from blood circulating in the breast The uncertainty lies in the actual mechanism by which this transformation is accomplished Alcock (1936) believes that the protein molecule may be built up in toto from simple chemical groups and then aromatic nuclei added later Most authorities however, still believe that intact individual amino-acids must first be acquired as food or else synthesized in the body As regards homologous organs from different animals the protein formed from mixtures of amino-acids is characteristic of each type of animal host Foreign protein is not incorporated directly into the natural protoplasm Indeed when foreign protein is injected into the organism, the nitrogen of it may be eliminated in the urine Mendel and Rockwood (1904-5) showed also that in this case there may be in addition a "toxic destruction of the natural body protein, which may be related to anaphylactic shock Similarly Abderhalden and Roske (1926) showed that the injection of dog's blood into a dog results in less extra excretion of nitrogen than does the injection of human blood into a dog

To date our best information on newly formed protein consists in studies of the plasteins previously mentioned From substrates containing peptone or albumose it has been possible to produce materials which have many of the properties of protein including antigenic activity

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This process of amino acid catabolism is insolubly connected with the liver and with the formation of urea In the normal animal Levene found that practically all of the amino acid nitrogen not retained in the body was excreted in the form of urea or of ammonia derived from it Protein food to be sure yields acid products which must in part be neutralized in the kidney by ammonia and this ammonia nitrogen comes from the amino-acids Nevertheless the amino nitrogen probably is first turned into urea in the liver and then back into ammonia in the kidneys a possible intermediary being arginine (Krebs and Henseleit 1932)

Van Slyke Cullen and McLean (1915) found that early in the absorption of a protein meal the liver begins to transform into urea the first amino-acids that reach it via the portal vein This was true even in the previously fasted animal Van Slyke with Cullen (1917) also found that during the ingestion of meat by dogs the urea content of the blood increased about 2 mg per cent in passing through the liver The fact that amino-acid nitrogen showed the reverse change indicated this material as the source of urea in protein breakdown Similar results were found by Witts (1929) who studied in man the effects of the ingestion of 25 gm of glycine upon the blood amino nitrogen and the blood urea As appears in Fig 8 the amino nitrogen in the blood of men after such a meal rises 2 to 6 mg per cent to attain a peak in about two hours Meantime there is a slower increase in urea formation which reaches its high level somewhat later

It now seems probable that the liver is the chief site of urea formation in man Jansen (1915) has confirmed the older observations that when isolated

dogs livers are perfused with solutions of amino-acids urea is formed Van Slyke and Meyer (1913 c) also found that the liver of the intact animal can destroy amino acids at a rate very much greater than can the muscles They found too that the blood passing through the liver takes from it about as

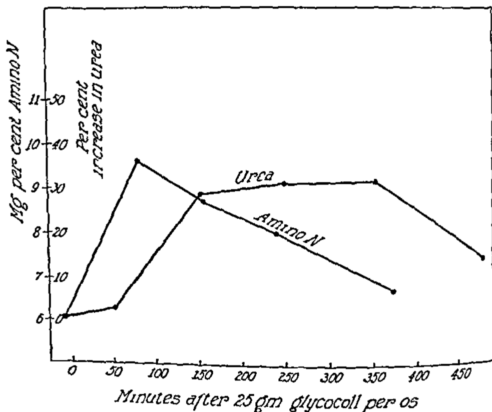


FIG 8 Effects of ingestion of 25 grams of glycocoll upon the blood amino nitrogen and the blood urea of a normal man After Witts (1929 p 479)

much nitrogen in the form of urea as it gives to it in the form of amino-acids Much controversial evidence has been accumulated however, as to which tissue is the more important anatomical site of this chemical reaction in the intact animal Among others Folin and Berglund (1922) maintained that the liver was not especially ordained for urea formation but that the process occurred in all cells just as does the consumption of oxygen Bollman Mann and Magath (19 4) however provided striking evidence in favor of the liver as the chief site and probably the only important source of urea formation in mammals They found that in animals from which both kidneys and liver had been removed the blood urea remained constant If the kidneys were removed but the liver left intact the blood urea rose rapidly

The Combustion of Protein

Carbohydrate and fat may be completely oxidized artificially in the laboratory to carbon dioxide and water. The amounts of oxygen consumed and of carbon dioxide produced may be determined in vitro and these values applied directly to the living organism.

Likewise the heat evolved in the calorimetric bomb may be used in computing the energy of oxidation to be expected when such food stuffs are burned in man. Not so with protein or amino-acids. Their oxidation in the calorimetric bomb to nitric acid or even free nitrogen gas does not reproduce the quantitative transformation into urea found in mammals. In calorimetric measurements by the indirect method therefore the protein catabolism must be measured by the urinary nitrogen excretion or else a uniform constant value for this value must be assumed.

The quantitative relationships involved are shown in Table VI.

TABLE VI

CALORIC VALUE OF FOOD STUFFS
From Peters and Van Slyke (1931, p. 6)

One Gram of Substance	O_2 absorbed	CO_2 formed	R.Q.	Calories		Calories	
				Rubner	Loewy	O_2	CO_2
	cc	*cc*				*1 liter*	*1 liter*
Protein	966.3	773.9	0.801	4.10	4.316	4.485	5.579
Urinary nitrogen	5939.0	4757.0	0.801	25.63	26.54	4.485	5.579
Fat	2019.3	1427.3	0.707	9.3	9.461	4.686	6.629
Starch	828.8	828.8	1.000	4.1	4.182	5.047	5.047

THE SYNTHESIS OF NON-PROTEIN NITROGENOUS SUBSTANCES

In addition to forming protein amino-acids may also serve as the starting material for the natural synthesis of creatine and of purines. Because the amino-acid arginine, like creatine, contains a guanidine nucleus it seems likely that it may be the mother substance of creatine and creatinine as suggested in a subsequent section.

Ackroyd and Hopkins (1916) fed histidine and arginine to dogs and observed an increase in the output of allantoin, the natural end stage of purine catabolism in dogs. Similarly Rose and Cook (1925) found other evidence that the amino-acid histidine serves for purine synthesis.

Proteins in Relation to Hormones and Enzymes

Willcock and Hopkins (1907) suggested also that some of the hormones are derived from amino acids containing aromatic nuclei This has been made more probable by Harington s work (1926) on thyroxine itself an amino-acid, and on diiodotyrosine another amino-acid Both of these iodine substituted molecules are integral parts of the thyroid protein thyroglobulin The structural similarity of adrenin to phenylalanine and to tyrosine suggests a similar relationship

The proteins also furnish the albuminous part of the molecular structure of enzymes As described earlier both pepsin and trypsin can be isolated as crystalline proteins and so can also the protein urease from jack bean meal Stanley s crystalline virus (1935) of mosaic disease in tobacco likewise is a protein In the case of the yellow respiratory enzyme of Warburg a protein is combined with vitamin B to form the larger molecule which catalyzes oxidations in cells (Theorell 1935) Protein thus serves as the carrier for active groups as discussed in a previous section Kuhn (1936) has shown that when this protein carrier is separated from the prosthetic group, the enzymic activity is lost Indeed the so-called destruction of most enzymes by heat correlates well with the similar behavior of the non specific heat coagulable proteins

Conversion of Protein into Carbohydrate or Fat

That a high meat diet may yield body carbohydrate has been established by two types of observations The first involves the determination of the respiratory quotient and caloric consumption Such an experiment was made by Williams Riche and Lusk (1912) who fed a dog 1200 gm of meat They found by following the oxygen consumption and the heat production that for 14 hours thereafter carbon was retained in the form of either glucose or glycogen in the organism The other type of observation is typified by the classical results of Lusk obtained in diabetic animals Such experiments show that protein yields 58 per cent of its weight as urinary sugar, as described later on in this chapter

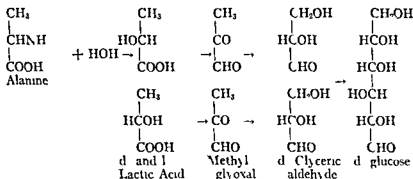
The formation of fat from protein is more difficult to demonstrate It apparently occurs in mammals when and only after body cells are saturated with glycogen Atkinson Rapport and Lusk (1922) found that ordinarily meat caused the deposition of glycogen in dogs but that when carbohydrate was given at night then meat in the morning would yield observations indicative of fat formation In this connection the observations of Weinland (1908) are of interest He found that the pulp of crushed larvæ could produce higher fatty acids from peptone

Formation of Sugar and Ketones from Amino-Acids

In Lusk's laboratory (Reilly, Nolan and Lusk, 1898) protein was fed to a dog which because of phlorhizin poisoning was incapable of retaining glucose. The resulting changes in sugar excretion and in the dextrose nitrogen (D : N) ratio indicated that approximately 58 per cent of protein was transformed into glucose. This left 46 per cent for ketone body formation, i.e., 58 per cent plus 46 per cent equals 104 per cent protein including the water of hydrolysis. That sugar originated from individual amino acids was shown in dogs by Lusk and his collaborators (Stiles and Lusk, 1903) and by Dakin (Dakin and Dudley, 1914) who fed isolated amino-acids to phlorhizinized dogs.

It was shown by these experiments that all the carbon in glycine and alanine appeared as glucose and similarly over half the carbon in aspartic and glutamic acids. Arginine, proline, cystine and serine likewise formed glucose. Similar results have been obtained in the metabolism of protein by experimentally depancreatized animals and by patients suffering with severe diabetes mellitus.

The possible chemical reactions by which amino-acids are transformed by the liver into glucose have been discussed by Dakin, who suggested the following schema to express this relationship:



(After Lusk, 1928, p. 233)

Likewise Dakin and Dudley (1913) showed that the surviving livers of dogs formed considerable amounts of acetone and acetoacetic acid when perfused with solutions containing histidine, phenylalanine or tyrosine. Knoop (1908) has suggested the following chemical reactions as the mechanism whereby this transformation may be accomplished:

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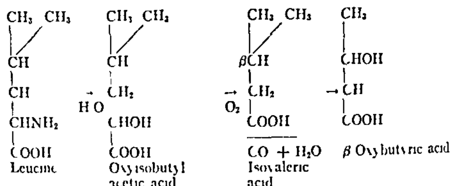
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are representative values from Williams Riche and Lusk (191) combined with similar observations made by Aub and DuBois in abnormal men (1917) It will be observed that in man for every extra 100 calories increase in the protein catabolism the heat production increases about 30 calories In man however it is difficult to produce the marked increase in metabolism e g over 90 per cent found in carnivorous animals The constancy of this specific dynamic action is demonstrated by the observations of Weiss and Rapport (1924) who obtained with a dog the following increases of metabolism in four experiments distributed over a year s time 28 6 9 9 31 2 and 27 5 per cent Furthermore Plummer Deuel and Lusk (19 6) obtained results identical to Rapport s under similar condition

Despite many physiological experiments the mechanism of the specific dynamic effect remains unexplained as Wilhelmj (1935) recently has concluded after an exhaustive survey It appears not to be due to deamination Nor can it be explained on the basis of synthetically formed glycogen or fat Furthermore Hoobler (1915) showed that the mere absorption of amino-acids and their rebuilding into new protoplasm does not increase the metabolism It appears to be a general tissue phenomenon because muscle tissue alone exhibits the effect as was demonstrated by Rapport and Katz (1927) who showed that the oxygen consumption of muscles in an isolated limb increased 35 per cent when perfused with blood reinforced with glycin The rôle of the liver in the phenomenon is not clear Aub and Means (1921) found that human cases of liver cirrhosis showed the highest re ponse to protein but Mann (Mann Wilhelmj and Bollman 1927) was unable to find such an effect in hepatectomized dogs

Numerous attempts have also been made to discover what common property or constituent of proteins produce the specific dynamic effect Thus Rapport (1924) showed that approximately the same dynamic action is produced by the various proteins in beef codfish and chicken and by casein gliadin and gelatin Likewise Falta Grote and Staehelin (1907) showed that not only casein but also the amino-acids resulting from the hydrolysis of casein produce the same specific dynamic action as does meat protein when fed to a dog Various amino-acids and combinations thereof also have been tested for their ability to produce this phenomenon Atkinson and Lusk (1918) found that neither glutamic acid a partic acid nor asparagin have a dynamic action Other amino-acids produce a positive effect but in varying degree Rapport and Beard (1927) gave 10 gm of each of various amino acids to a small dog with the following increases of basal metabolism for glycin 29 per cent for alanine 20 per cent for leucine 10 per cent for phenylalanine 39 per cent and for tyrosine 20 per cent Rapport and Beard reported further that the specific dynamic action of gelatin and meat may be accounted for entirely by the summated effect of five component acids In the case of the dipeptide glycyl glycin Plummer Deuel



(After Lusk 1928 p 235)

On the basis of this and similar data Shaffer (1923) has calculated the ketogenic antiketogenic values of diets containing protein Analogous figures appear in a paper on the Woodyatt (1921) ratio and in Joslin s book (1935) on diabetes

The Specific Dynamic Action of Protein Food

In 1852 Bidder and Schmidt (1852) gave a large protein meal to a starving cat and reported a doubling of the oxygen consumption Since then many confirmatory observations have been made of this phenomenon In Table VII

TABLE VII

The Specific Dynamic Action of Protein in Man
From Lusk (1928 p 284)

Subject	Food	Body Weight	Every Extra 100 Cals Contained in Protein Metabolized Increases the Heat Production in Calories
	Gm	Kg	
Normal man	Casein 50 gm		67
	100		56
	150		83
	200		74
Normal man (W B)	Meat 600		82
Normal man (S K)	660	49 5	6
Legless man (H J)	660	55 0	7
Achondroplasia (R de F)	662	41	71

In excessive water drinking according to Abderhalden and Bloch (1907) there is a transitory washing of nitrogen into the urine but this is restored when water balance is righted The rule that nitrogen equilibrium is normally maintained has therefore a certain limit of elasticity Within this variation a healthy individual may go for years without great change in weight even though no particular attention is paid to diet

Rubner (1911) pointed out that the requirement of nitrogen in the food might be apportioned in several quotas A repair quota of protein is needed to compensate for wear and tear In addition young individuals require a growth quota' for building protoplasm in multiplying cells Similarly the adult patient after a wasting disease or after fasting requires an improvement quota' to replenish protein stores When protein is given in excess of building requirements and is burned for fuel Rubner spoke of this excess variety as the dynamic quota

The protein reserves of the body are enormous if regarded merely as reserved for replacement of wear and tear Rubner estimated that a man containing 2100 gm of protein nitrogen might lose over 1100 gm before death On a pure carbohydrate diet high in calories the man would live over a year because little or no protein would be expended in the dynamic quota Of course with a loss of 30 per cent of body protein marked weakness would be present It is not known whether deposit or improvement protein comes from the living protoplasm or whether it merely represents a special store of protein in cells analogous to glycogen in the liver It is possible that this material is distributed by way of the liver Indeed Smith Belt and Whipple (1920) found that the presence of the liver was essential to a rapid renewal of serum proteins in the dog

Boothby showed that this deposit protein varied considerably with thyroid activity Its extent was measured by Deuel (Sandiford Sandiford Deuel and Boothby 1920) who partook of a protein free diet for sixty three days during which time the partition of nitrogen in the urine was studied as well as his heat production The minimal excretion of total nitrogen in the urine during a period of thirty days on the high carbohydrate diet was 2 1 grams per 24 hours After even greater exhaustion of the deposit protein by the administration of thyroxine the nitrogen excretion was lowered to 1 8 gram or 0 024 grams per kilo No noticeable deleterious effects followed a total loss of some 290 grams of deposit protein nitrogen, equivalent to 1 8 kilos of dry protein The change in nitrogen elimination was due almost entirely to variation in the urea elimmated whereas the sulphate remained extremely constant There was a rapid fall in the basal metabolic rate during the first week of the protein free diet Thereafter the basal metabolic rate remained practically constant until the subject again resumed a high protein diet whereupon the basal metabolism was

and Lusk (1916) found the same effect as with glycin It is still unexplained why glycin, added to gelatin has no extra effect

IV

NUTRITION AND PROTEIN

Fluctuations in Nitrogen Balance

Nitrogen Metabolism and Nitrogen Equilibrium

The normal adult loses daily an amount of nitrogen equal to the nitrogen content of his diet Under such circumstances the individual is said to be in nitrogen equilibrium For practical purposes this state ordinarily is attained when the urinary nitrogen is less than the dietary intake by 1 3 grams i e, the amount of the fecal nitrogen If the nitrogen excretion exceeds the intake, the nitrogen balance is said to be negative, because the individual is losing nitrogen from the body stores On the other hand, when nitrogen is retained the balance is said to be positive

If the non protein nitrogen of the body fluids remains constant, a positive nitrogen balance usually means the formation of new protein, and conversely a negative balance means that the tissue is being destroyed The normal adult who has attained full growth usually is in a state of nitrogen equilibrium The body has little capacity for the storage of surplus nitrogen and in normal adults on abundant diets the urinary nitrogen varies directly with the dietary nitrogen To be sure, the equilibrium is not absolutely independent of the protein intake If the nitrogen of the diet is increased, this change will result in some accumulation of nitrogen in the body for several days until a new equilibrium state is attained Thereafter the nitrogen elimination will increase steadily to compensate for the new diet and equilibrium will be established again with a somewhat higher concentration of non protein nitrogen in the body fluids The nitrogen thus taken up and given off apparently is in the form of a reserve food protein as contrasted with the living cellular protein, for Rubner (1902) found that protein added in this manner did not increase the amount of living substance as indicated by the total metabolism of the body

A true addition of living protein may be induced in adults by physical training The phenomenon is commonly observed in athletes, who during the training season after perhaps an initial loss put on a few pounds weight of muscle up to a definite limit beyond which they cannot go Inversely muscular weight so gained may be lost again through inactivity After bleeding there is a retention of nitrogen and likewise as Schrader (1894) showed, after menstruation in women This retention of course represents repair of lost tissue

In excessive water drinking according to Abderhalden and Bloch (1907) there is a transitory washing of nitrogen into the urine but this is restored when water balance is righted The rule that nitrogen equilibrium is normally maintained has therefore a certain limit of elasticity Within this variation a healthy individual may go for years without great change in weight even though no particular attention is paid to diet

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definitely elevated above normal level Otherwise no noticeable physiological disturbances resulted from the prolonged ingestion of protein free food Deuel, Sandiford Sandiford and Boothby (19 8) showed also that by administering thyroxine even after such depletion of reserve protein, one might eliminate further reserve protein

Fecal Nitrogen Excretion

In studies of protein metabolism the practice has been widely adopted of considering that one tenth of the ingested protein escapes assimilation and that its nitrogen, therefore, appears in the stools Studies by Smith (1926) however indicate that fecal nitrogen is not directly related to food nitrogen it remains relatively constant despite wide variation in the amount of dietary protein Fecal nitrogen ordinarily varies only in severe watery diarrheas or when there is a deficiency of the proteolytic digestive ferments

Nitrogen is lost also in the sweat chiefly as urea and ammonia so Graham and Poulton (1912-3) found About 0 3 gm a day of nitrogen ordinarily is lost in this way although marked sweating may raise this figure to about 1 gram Kestner (1923) estimated that 1 5 to 3 4 gm of nitrogen, chiefly as protein may be lost in the menses

Urinary Nitrogen Excretion

The chief channel by which ingested nitrogen is lost is of course the urine Usually a normal adult excretes daily an amount of nitrogen equivalent to that ingested provided the protein intake is adequate but not excessive Under such conditions urinary nitrogen serves to measure nitrogen catabolism and also nitrogen ingested The normal urine contains negligible amounts of protein and in man urea and ammonia constitute the two chief forms of excreted nitrogen Urea usually accounts for 75 to 85 per cent of the total nitrogen With an ordinary mixed diet the excretion of ammonia nitrogen is about 0 5 to 0 7 grams per day or 4 to 5 per cent of the total urinary nitrogen On a meat diet the trend of metabolism is acid in the sense that relatively large quantities of phosphoric sulphuric and uric acids are produced The first two of these it will be noted are strong mineral acids Phosphoric acid arises from the destruction of the nucleins the phosphoproteins and the phospholipins Sulphuric acid is the end product of the oxidation of sulphur Accordingly ammonia excretion may rise considerably on a pure meat diet and the urea plus ammonia may reach 75 per cent of the total urinary nitrogen

The sum of urinary urea and ammonia is a good guide to the rate of protein catabolism, whether the source be ingested food or the animal s own tissue

Usually in adults it is equal to the protein nitrogen in the daily diet i e some 10 to 15 grams of nitrogen daily In a fasting individual however, this would represent the loss of a pound of flesh, because one gram of nitrogen represents about 30 grams of muscle

Folin (1905) showed that, when the protein catabolism diminished both the relative and absolute amounts of these two substances decreased In Table VIII is shown the effect of an extremely low protein intake upon the nitrogen

TABLE VIII

THE EFFECT OF EXTREMELY LOW PROTEIN INTAKE ON NITROGEN EXCRETION AND BLOOD NON PROTEIN NITROGEN

After Smith (1926 pp 20–21) revised by Peters and Van Slyke (1931 p 272)

		Grams per day urine nitrogen as							Urine Nitrogen as per cent of Total Nitrogen							
Days	Feces N	Total	Urea	NH_3	NH_3 + Urea	Uric acid	Creatinine	Undetermined N	Urea	NH_3	NH_3 + urea	Uric acid	Creatinine	Undetermined N	Blood N P N	
7	1 02	12 03	10 02	0 50	10 52	0 15	0 68	0 68	83	4	87	1	6	6	27	Unrestricted diet Averages
6	0 85	4 85				0 13	0 64									N intake 0 27 gram per day
8	0 73	3 45				0 18										N intake 0 80 gram per day
5	0 84	2 17	0 81	0 34	1 15	0 12	0 57	0 34	37	16	53	6	26	16	17	N intake 0 97 gram per day
3	0 87	1 99	0 48	0 33	0 81	0 14	0 59	0 45	24	17	41	[illegible]	30	23	15	N intake 0 70 gram
2	0 91	1 63	0 32	0 20	0 52	0 12	0 56	0 44	20	12	32	7	34	27	13	N intake 0 36 gram per day
3		7 17	5 45	0 33	5 78	0 12	0 51	0 74	76	5	81	2	7	10		Return to regular diet

excretion of a normal man It will be noted that urea and ammonia which together usually make up 80 per cent or more of the total nitrogen may fall to 30 per cent. of the total On the basis of such findings Folin distinguished between endogenous protein metabolism of body tissue (cf Rubner's ' wear and tear quota) and exogenous protein metabolism (cf Rubner s dynamic quota) derived chiefly from ingested protein Folin interpreted the en

dogenous catabolism as representing that of the living protoplasm, whereas the exogenous catabolism meant ingested protein.

PROTEIN CATABOLISM IN STARVATION

Nitrogen Excretion in Total Starvation

When no food is supplied, the organism rapidly uses up the available stores of liver glycogen and under such circumstances there is not at first a rapid breakdown of protein. Later protein is destroyed rapidly, but as starvation proceeds there is a steady drop in nitrogen excretion. Fat contributes the major part of the energy, but serious ketosis is prevented by the antiketogenic effect of the smaller moiety of protein burned. Benedict (1907) has shown that in prolonged fasting about one-eighth of the energy is supplied constantly by protein. The effect is as if the individual subsisted upon a constant mixture of fat and protein derived from his own flesh. Similarly Succi's urine contained (Freund, E. and O., 1901) 11 gm. of nitrogen on the fifth day of fasting but only 3 gm. on the twenty-first day. The sulphur excretion was about one-sixteenth that of the nitrogen as against one-fourteenth found by Wilson (1923) for meat protein. Incidentally albumin frequently is found in the urine during fasting and must be taken into account.

Phosphate excretion in starvation is greater than the nitrogen would indicate, because of loss of phosphate from bone. Thus the ratio $\frac{N}{P_2O_5}$ in meat is 7.6 but Succi's urine showed values of 5.7 to 4.2.

The duration of life in starvation depends upon the quantity of fat present in the organism at the start, as E. Voit (1901) found. He showed also that the extent of protein catabolism in starvation depends upon the amount of fat in the body. When fat stores become low, then over 98 per cent. of the total energy may be derived from protein in the "premortal rise" of protein metabolism, according to Mangold (1926). Likewise, when protein is the chief source of energy more body weight is lost than when fat is the chief source of energy. Indeed in such extreme cases over eleven times more weight is lost than when fat alone is burned. This is true because the metabolism of 100 gm. of flesh yields only 80 calories in contrast with the 930 calories liberated when 100 gm. of fat are oxidized.

Why does prolonged starvation cause death? It is certainly not due to exhaustion of all available fat. On the other hand it appears to be associated with loss of animal protein. Schulz and Mangold (1906) let a well nourished dog fast for 27 days, at which time its life appeared in danger. In the next five days 400 c.c. of milk and 1200 gm. of meat were given. Thereafter the

dog starved for 61 days. When the fasting dog contains considerable fat it is found that on feeding the animal any protein in the food is retained in large measure even though the diet be meagre. Similarly Howe and Hawk (1911) showed that a repeated fast causes less protein loss, the ratio of the successive losses being nearly 2 : 1 in one such double experiment.

During starvation the blood proteins are not affected greatly. T. B. Robertson (1912–13) found a slight increase in globulin in the dog and the cat, whereas there was increased albumin in rabbit, ox and horse.

Specific Nitrogen Starvation

When an animal is given a high caloric diet free of protein the animal is said to experience specific nitrogen starvation. From Table IX it is evident

TABLE IX

URINARY NITROGEN EXCRETION SHOWING PROTEIN SPARING
Adult man after fasting 14 days received daily 300 c c of cream and 400 grams of starch. From Cathcart (1907 p 121)

	Total N Gm	Urea N Gm
Day 14 of starvation	7 78	5 99
" 1 on cream starch diet	7 43	5 80
" 2	3 58	2 29
3	2 84	1 ,6

that protein breakdown during total starvation is by no means minimal. It is evident on the other hand that when carbohydrate is supplied the nitrogen excretion is halved. This protein sparing action of non protein food is thought to be due simply to the diminished need for protein as an antiketogenic source of energy. With the diminished protein catabolism the non protein nitrogen of body fluids falls. On the other hand when abundant amounts of carbohydrate and fat are supplied but in the total absence of protein in the diet one may observe the minimum or endogenous nitrogen catabolism. This wear and tear quota of protein breakdown may be reflected in a daily urinary nitrogen excretion of only 0 025 to 0 04 grams per kilo of body weight. The total loss corresponds to the loss of less than 0 35 gm of protein per kilo per day. Meanwhile fecal nitrogen remains nearly unchanged at about a gram per day.

Krause (1926) states that to attain such a low minimum the caloric value of the diet must be at least twice the basal caloric requirement. Otherwise

dogenous catabolism as representing that of the living protoplasm, whereas the exogenous catabolism meant ingested protein

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The duration of life in starvation depends upon the quantity of fat present in the organism at the start, as E Voit (1901) found He showed also that the extent of protein catabolism in starvation depends upon the amount of fat in the body When fat stores become low, then over 98 per cent of the total energy may be derived from protein in the "premortal rise of protein metabolism according to Mangold (1926) Likewise when protein is the chief source of energy more body weight is lost than when fat is the chief source of energy Indeed in such extreme cases over eleven times more weight is lost than when fat alone is burned This is true because the metabolism of 100 gm of flesh yields only 80 calories in contrast with the 930 calories liberated when 100 gm of fat are oxidized

Why does prolonged starvation cause death? It is certainly not due to exhaustion of all available fat On the other hand it appears to be associated with loss of animal protein Schulz and Mangold (1906) let a well nourished dog fast for 27 days at which time its life appeared in danger In the next five days 400 c c of milk and 1200 gm of meat were given Thereafter, the

pick a proper diet and accumulates statistical data from healthy men the second determines the minimal protein intake which will yield nitrogen equilibrium in apparent health the third determines the maximal protein intake that is not injurious and looks for evidence of increasing vigor with increasing protein consumption Both strict vegetarians and avid flesh eaters support their contentions with subjective evidence of a sense of well being

By averaging the nitrogen excretions of many laboring men Voit (1881) obtained a daily value of about 1 7 gm per kilo daily or 118 gm of protein for the average man Similar figures were obtained in 1903 by Lichtenfelt Rubner (127 gm) and Atwater (125 gm) (Lusk 1928 p 448) Higher figures are found for men at hard labor Woods and Mansfield (1904) reported 164 gm daily for lumbermen

Controlled experiments however have indicated that much less protein may be adequate Siven for instance found that he could maintain himself in nitrogen equilibrium for a short period on less than 0 5 gm of protein per kilo (1901) Chittenden also maintained nitrogen equilibrium in himself for many months on a bare 40 gm of protein daily (1904) During this time he led an active life Other experiments by Chittenden extending from five to nine months indicated that a daily nitrogen intake of 10 gm or less i e 63 gm of protein or less was not detrimental to health Lusk (1928 p 455) even stated that 50 gm of protein containing 8 gm of nitrogen are apparently able to maintain the adult body machine in perfect repair

High protein diets often have been decried as injurious but on this subject there are conflicting opinions To be sure Newburgh and Clarkson (19 3) produced atherosclerosis in rabbits after the prolonged use of diets containing 36 per cent protein Mackay Mackay and Addis (1927) likewise produced renal hypertrophy but no kidney damage There is however no convincing evidence that these observations apply to men At least two serious studies have been made of carnivorous man in the Arctic regions In 1913 Krogh and Madam Krogh (1913) published investigations on the Greenland Eskimos whose diet was chiefly meat W A Thomas summarizes similar observations as follows The Greenland Eskimo on a carnivorous diet exhibits no increased tendency to vascular or renal disease This diet furnishes him with vitamins adequate for protection against rickets (1927) Similar observations have been made upon Vilhjalmur Stefansson who has lived many years in the Friendly Arctic (1921)

Since Rubner many observers have confirmed the finding that climate and temperature influence the need for protein In hot weather the specific dynamic action of ingested protein increases the heat production and with it the amount of perspired water On the contrary in cold weather the increased heat from ingested protein may be of benefit

the protein sparing action of the carbohydrate and fat will be progressively less as the caloric value of the diet is diminished Here again, urinary nitrogen excretion slowly diminishes after the incomplete diet is started Smith (1926) noted a steady drop for over three weeks as if each successive decrement of protein was given up less readily than the last

Some investigators have conceived of the stores of protein drawn upon in nitrogen starvation or in total starvation as analogous to glycogen stored in carbohydrate metabolism For this reason the term "deposit protein" (Lusk 1928 p 89) was suggested to distinguish protein available for combustion from the indispensible nitrogenous tissue components in cells There is probably as yet insufficient evidence to justify this distinction In starvation or in very low protein diets the muscles yield up protein to the circulation presumably in the form of readily diffusible polypeptides or amino-acids

In the case of the spawning salmon Miescher (1896) showed that the genital organs of both male and female develop greatly despite the starving condition of the animals The muscles may lose in fact 55 per cent of their weight, yet Miescher found no indication of actual destruction of muscle fibres in the emaciated animals In mammals, moreover, Voit (1901) showed that the preliminary ingestion of meat increased the expected nitrogen excretion for several days fasting thereafter He, therefore, distinguished between "circulating protein" which could be mobilized and burned, and "organized protein", i e the resistant living protein

Furthermore Kumagawa (1894) showed that after prolonged starvation the weight of cardiac muscle remained little changed despite marked loss of weight in the skeletal musculature It is evident that urinary nitrogen in starvation may represent only a part of the protein being removed directly from skeletal muscles

Protein Requirements

A man cannot eat sufficient protein alone to satisfy his caloric needs and maintain nitrogen equilibrium Even in the case of the dog Voit (Lusk, 1928 p 187) found that five times the fasting protein breakdown must be fed to establish nitrogen equilibrium Likewise K Thomas (1910) found that a man may consume as much as double his fasting excretion and yet fail to establish nitrogen equilibrium Evidently the caloric value of protein is by no means the chief factor which decides how much an individual needs daily

The protein requirement for adult men has been the subject of great controversy The problem is obscured by fads and fancies for even scientists are not free from dietary preference and prejudice Students of this subject are of three sorts the first relies upon the innate instinct of the untutored man to

'Optimum' Protein Requirement

Although the foregoing studies have demonstrated that the minimum protein requirement of adults may be as low as 0 5 to 0 7 gm of protein per kilogram of body weight per day it is generally assumed to be better to give more for optimal metabolism Mitchell (1926) has pointed out that there is no irrefutable experimental justification for this assumption of an optimum intake of protein Evidently optimum protein intake is an arbitrary assumption On the other hand Van Slyke points out (in a previous edition of this work) that such experiments as those of Hinhede cited above have been conducted for relatively short periods as compared with the life span of the subjects and usually have dealt merely with the maintenance of adult males Particularly for the periods of growth and of gestation and lactation in the female it would seem that consideration should be given to the conclusion of McCollum Simmonds and Parsons (1921) arrived at after experiments on animals extending over the entire period of growth reproduction and lactation viz that health and vigor are promoted by a liberal intake of protein of good quality better than by any diet in which there is parsimony with respect to this dietary factor

It is interesting in this connection that three centuries ago 'meat and drink' was the standard phrase for nourishment Since that time carbohydrate has assumed an all important rôle in the diet of great masses of people Now a days protein rarely accounts for more than one-sixth of the energy in diets of normal individuals

Protein Requirement for Growth

The chief constituent of the body cells is protein and during normal growth protein is continually retained by the organism and synthesized into tissue substance McCollum (1914) found indeed that the rapidly growing pig may incorporate into its body two-thirds of the nitrogen it ingests Armsby and Moulton (1925) have summarized the efficiency of protein storage in growing animals raised for meat and find retentions over weekly periods as high as 80 per cent of the food proteins The more slowly growing child retains proportionately smaller amounts of nitrogen as long as growth continues Only when maturity is reached does the protein content of the body assume a fixed level subject to very minor fluctuations unless disease intervenes In growing children the problem of optimum protein intake is very complicated Rubner and Heubner (1905) found that an infant could be maintained on a diet in which only 5 per cent of the energy was supplied by protein In their observations when an additional 2 per cent of protein-equivalent was supplied it was

The Effect of Non Protein Foods on Protein Requirement

On closer study it is clear that the minimum protein requirement for nitrogen equilibrium depends upon the amounts of non protein food concomitantly supplied in the diet

Carbohydrate — When the diet contains moderate amounts of carbohydrate it is possible to establish nitrogen equilibrium at a much lower level than when protein alone or protein and only fat, are eaten

Indeed Zeller (1914) reduced gradually the carbohydrate in a diet containing very low protein and found that the nitrogen excretion was not significantly altered until less than 10 per cent of the total calories were in the form of carbohydrate

At this juncture traces of acetone appeared in the urine and simultaneously the nitrogen excretion increased When carbohydrate was eliminated altogether the minimal protein requirement increased to the starvation level of about 60 gm of protein daily

Fat — The effect of dietary fat upon protein metabolism is essentially an indirect one Richardson and Mason (1923) showed that its effect is simply to replace body fat or protein which otherwise would be burned When fed alone it does not spare protein C Voit (1881) found that when abundant fat is fed alone, without carbohydrate or protein loss of body nitrogen occurs exactly as in total starvation Combined with carbohydrate in the diet, however, it reduces markedly the amount of carbohydrate required to spare protein breakdown

Alcohol, likewise, can protect body protein and to this end may be used in limited amounts in place of fat or carbohydrate of equal caloric value Thus Atwater and Benedict (1902) replaced 56 gm of fat with 72 gm i e, 500 calories of alcohol and found that 98 per cent of the alcohol was burned Similarly Neumann (1902) was able to demonstrate that when 100 gm of alcohol were added to a mixed diet containing 2590 calories the human subject reverted from nitrogen equilibrium to a positive balance a retention of 2 gm of nitrogen daily taking place

Higgins Peabody and Fitz (1916) found however that alcohol lacks the ability of carbohydrate to prevent acidosis and therefore cannot replace all the carbohydrate in the diet Furthermore Stillman (1919) found that its usefulness was distinctly limited by its toxic effect Sommerkamp (1924) showed nevertheless that it was burned and did spare protein during muscular exercise

Amino Acids — The effect of feeding amino acids is somewhat obscured by the specific dynamic effect previously discussed on earlier pages of this chapter

and 0 047 grams per kilo and were not closely correlated with the total caloric turnover

Work and Protein Requirement

Whether or not protein is used in muscular work depends as Shaffer (1908) showed upon the availability of non protein food If sufficient food be allowed change in muscular activity has no effect upon protein metabolism or upon

TABLE X

Minimal Nitrogen Metabolism in the Two Sexes
From Lauter (1922 pp 54-61)

	Man 70 Kg	Girl 11 Yrs	Girl 15 Yrs	Pregnant Woman Age 19 Yrs (9th Month)
Urine N gm	2 66	1 01	2 35	2 09
Urine + feces N gm	3 71	1 86	3 28	3 53
Urine N per kg gm	0 039	0 035	0 045	0 03
Total N per kg gm.	0 053	0 046	0 063	0 058
Calories of basal metabolism (Du Bois) in per cent		2 2	1 6	2 0

creatine elimination It is clear that energy for muscular work usually is not derived from protein metabolism but from the combustion of sugar and fat

On the other hand Hindhede (1913) demonstrated that nitrogen and caloric requirements advance together with heavy work when the supplies of fat and carbohydrate in the diet are inadequate He therefore suggested that to guard against this contingency it might be desirable to supply extra protein to heavy workers Likewise Cathcart (1925) has suggested that a profound flux of muscle metabolism may occur in exercise but that newly released amino-acids usually are resynthesized into new protein without appreciable loss of nitrogen in the urine Similarly Campbell and Webster (1922) found 10 3 gm of urinary nitrogen during severe work as against 8 0 gm at rest indicating a slight loss of nitrogen as the result of exercise Concomitant figures for creatine nitrogen were 0 74 and 0 93 gm respectively and Garry (19 6-7) found a similar rise of uric acid nitrogen from 0 063 gm at rest to 0 152 gm at work In short unless an ample supply of sugar is readily available the stress of severe work may lead to the utilization of some body protein Van Slyke in a previous edition of this series summarized the situation as follows The protein forms the substance of the bodily engine When the engine performs work

stored Likewise Schlossmann and Murschhauser (1913) found that an infant on a normal diet eliminated only 8 milligrams of nitrogen per kilo In short under favorable conditions nearly all available protein was used for growth Indeed Camerer (1902) showed that in a breast fed infant nine weeks old about 40 per cent of the protein ingested was stored

Krause (1926) concludes that the tendency for growth is so irrepressible that provided the caloric value of the food is sufficient the growing child will retain nitrogen if he is given anything in excess of the requirement for endogenous metabolism The endogenous requirement is much the same per kilo of body weight as in the adult It is at present unknown however how much protein in excess of this wear and tear requirement will promote maximum retention and growth In older children, however the rate of nitrogen retention above a minimal limit cannot be increased by increasing the protein intake Thus Ruotsalainen (1921) studied two boys aged nine and ten years who added one gram each daily, to their body substance on a mixed daily diet containing about 10 gm of nitrogen When the protein nitrogen in the diet was raised to 24 gm a temporary retention of about 7 gm of nitrogen daily occurred However ten days later when the reservoirs for deposit protein were filled the nitrogen retention was again about one gram daily even though the high protein intake continued

How much protein should the growing child be given? On an empirical basis it seems wise that for the present the standards of Holt and Fales (1921) be followed in normal children Holt and Fales formulated their standard simply on the basis of dietaries commonly in vogue They state that at one year the child should receive 4 gm of protein per kilo, and that from six years onward 6 gm of protein per kilo should be given throughout the growth period In special cases 2 gm of protein per kilo in younger children and nearer one gram in older adolescents probably will suffice if there is a special indication for limitation of diet The qualitative nature of dietary protein always must be the more carefully scrutinized as the quota of protein is reduced This is particularly true during the growth period when a generous assortment of the essential amino acids is needed Lysine for example which is not necessary for maintenance is indispensable for growth Holt and Fales recommend that two-thirds of the protein be given in the form of meat milk and eggs

Protein Requirement of Sex

From the data of Lauter (see Table X) it will be seen that kilo for kilo there is little difference in the minimum nitrogen metabolism of the two sexes Likewise the values for minimal nitrogen excretion obtained by Lauter (192) in children and pregnant women on high carbohydrate diets lay between 0 024

such a drain mammals may be kept in nitrogen equilibrium if calories enough be provided to satisfy the requirements of both mother and offspring. The protein supplied of course must exceed the sum of the milk protein and the mother's protein catabolism. Pure vegetable proteins alone even in large quantities often will fail to prevent wastage of maternal protein because the vegetable proteins do not contain enough of the amino-acids necessary for growth.

TABLE XI

PROTEIN CONTENT OF MOTHER'S MILK DURING LACTATION
After Holt, Courtney and Fales (1915, pp. 236–7)

	Colostrum period 1–12 days	Transition period 12–30 days	Mature period 2–9 months	Late period after 9 months
Per Cent of Protein	2.0–2.6	1.1–2.0	0.9–1.5	0.8–1.2
Total protein per day grams		5.5–12.0	7.2–13.5	

The simple addition of small amounts of milk may suffice to remedy this deficiency, although usually it is considered advisable to provide a generous supply of animal protein. If nitrogen equilibrium is not secured lactation continues for a time at the expense of the mother's tissues, but eventually the milk deteriorates in amount and in quality.

THE BIOLOGICAL VALUE OF VARIOUS PROTEINS

It has been demonstrated abundantly that there are nutritional differences between proteins and that mixtures of proteins are advantageous. To Osborne and Mendel and to the school of E. V. McCollum we owe much of our detailed knowledge of the nutritive value of various forms of protein and a rational explanation of this phenomenon. They showed that the nutritional difference between proteins rests in their respective contents of constituent amino acids. The foods ordinarily used by men are such mixtures that any ordinary diet would not likely be lacking in essential amino-acids unless the protein intake is low and also of poor quality from the biological standpoint. Of course, the more liberal and the more varied the protein supplied the less likely the diet is to lack a sufficiency of all the essential amino-acids. It is the special diets low in protein which must be scrutinized carefully if continued for long periods. The minimum protein requirement previously discussed accordingly assumed a careful control of its amino-acid content.

A striking example of an incomplete protein is zein, the chief protein of the

it burns an equivalent of fuel, but unless compelled to do so, it does not consume its own substance for energy production"

Of course protein may be used readily as fuel for work. Pflüger kept a dog in active condition over a long period on a diet of meat alone. Nevertheless protein is a rather inefficient fuel, because as Benedict and Murschhauser (1915) and Anderson and Lusk (1917) showed, the energy of mechanical work is superimposed upon that evolved from the specific dynamic action of protein.

During prolonged fasting Anderson and Lusk (1917) found that the energy of muscular contraction was supplied chiefly by the oxidation of fat. Only 3 per cent of the total metabolism in their observations could have arisen from protein.

As regards the physical fitness for work of individuals consuming varying quotas of protein, the observations of Lewis, Cotton and Rapport (1917) indicate no correlated change in muscular efficiency. They also found that removal of meat from the dietary for one week did not diminish the sense of well being. Prolonged deprivation of protein will, to be sure, lead to weakness but this symptom becomes marked only when evidence of incipient malnutrition appears, as will be described later.

Protein Requirement during Pregnancy and Lactation

Both pregnancy and lactation tend to produce a severe drain upon the maternal stores of protein. Hoffstrom (1910) calculated that in the last 23 weeks of pregnancy 310 gm. of nitrogen are retained, of which about one third is fetal. He computed that the nitrogen content of the developing ovum was about 10 gm. after 4 months and 75 gm. after 7 months. Furthermore Slemons (1904) showed that an average daily storage of about 3 gm. of nitrogen occurred late in pregnancy, and Harding and Montgomery (1927) estimated that such balances indicate the storage not only of fetal protein but also of maternal protein associated with increased muscular development. During eight days of the puerperium an average daily loss of 4.5 gm. of nitrogen occurs. This loss of maternal protein cannot be checked by a diet high in protein and in calories of non protein origin. The apparent wastage presumably is associated with involution of the uterus.

In lactation the mother must not only conserve her own body protein as well as possible but must also supply in the milk enough protein for the growth of her offspring. Harding and Montgomery showed that, when nursing women ingest only 5 to 8 grams of nitrogen daily, body protein is drawn upon even though the diet contains 4000 calories daily. This is readily understood from Table XI which indicates that for a long period the nursing mother must supply 7 to 14 gm. of milk protein daily. Hoobler (1917) has shown that even with

such a drain mammals may be kept in nitrogen equilibrium if calories enough be provided to satisfy the requirements of both mother and offspring The protein supplied of course must exceed the sum of the milk protein and the mother s protein catabolism Pure vegetable proteins alone even in large quantities often will fail to prevent wastage of maternal protein because the vegetable proteins do not contain enough of the amino-acids necessary for growth

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	Colostrum period 1–12 days	Transition period 12–30 days	Mature period 2–9 months	Late period after 9 month
Per Cent of Protein	2 0–2 6	1 1–2 0	0 9–1 5	0 8–1 2
Total protein per day grams		5 5–12 0	2 13 5	

The simple addition of small amounts of milk may suffice to remedy this deficiency although usually it is considered advisable to provide a generous supply of animal protein If nitrogen equilibrium is not secured lactation continues for a time at the expense of the mother s tissues but eventually the milk deteriorates in amount and in quality

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A striking example of an incomplete protein is zein the chief protein of the

maize kernel This protein is poor in the amino-acids tryptophane and lysine as shown previously in Table I Animals rapidly lose weight and die when maintained on a diet in which zein is the only source of protein The addition of the amino-acid tyrosine is without effect on the outcome Osborne and Mendel however were able to hold the weight of a rat constant for six months by adding tryptophane in an amount equal to three per cent of the zein When the zein was supplemented however, by both tryptophane and lysine, normal growth was obtained as shown in Fig 9 It is interesting that growth of

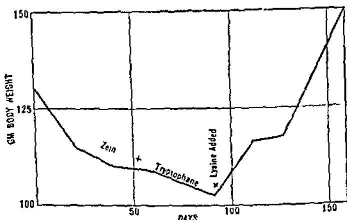


Fig 9 Effect of adding lysine and tryptophane to a diet deficient in these amino-acids After Mendel (1915 p 1543)

hair also was rapidly resumed when lysine was finally given Despite this striking effect of lysine when given with tryptophane, it was found that lysine alone will not prevent the decline which always occurs on a diet containing only pure zein for its protein constituent Both amino-acids are necessary

The maize kernel however contains another protein glutelin in about half the quantity of zein This glutelin is a "complete" protein i e it contains all the familiar amino acids and is therefore efficient in producing growth if administered in sufficient quantity In most diets of maize however there is not enough of this better protein to produce optimal growth which can be obtained only after adding a small supplement of milk protein i e lactalbumin plus lactoglobulin In the case of wheat Osborne and Mendel showed that similar growth effects could be produced with the two corresponding proteins, gliadin and glutein They found that dwarfed rats kept stunted for a year and a half on a diet of gliadin completed normal growth rapidly when a suitable diet was given

In the case of milk the two proteins of the curd and whey respectively casein and lactalbumin offer an interesting example of the complementary effect of two proteins The chief cause of the inferiority of casein is its poor content

of cystine Osborne and Mendel found that rats required for normal growth a diet containing 15 per cent of casein whereas 9 per cent was sufficient when reinforced with 3 per cent cystine In Table XII is given Mendel s summary of the value of various proteins for growth

TABLE XII

VALUE OF PROTEINS IN THE FUNCTION OF GROWTH
After Mendel (1915 p 1542)

Allow Growth		*Failure to Grow*	
Casein	milk	Legumelin	soy bean
Lactalbumin	milk	Vignin	vetch
Ovalbumin	hen s egg	Gliadin	wheat or rye
Ovovitellin	hen s egg	Legumin	pea
Edestin	hemp-seed	Legumin	vetch
Globulin	squash seed	Hordein	barley
Excelsin	Brazil nut.	Conglutin	lupin
Glutelin	maize	Gelatin	horn
Globulin	cotton seed	Zein	maize
Glutenin	wheat	Phaseolin	white kidney bean
Glycinin	soy bean		
Cannabin	hemp-seed		

From Lusk (1928 p 521)

The ability of dietary proteins to spare body protein has also been used as a means of measuring quantitatively the biological value of various proteins in food Thus Lauter and Jenke (1925) reduced the nitrogen excretion to the minimum wear and tear level and subsequently compared the relative protecting power of meat protein and vegetable protein upon this value They found that meat protein was more effective than vegetable protein in sparing the animal s stores of nitrogen

K Thomas (1909) suggested that in precise language the biological value of a protein be defined as the number of parts of body protein spared by 100 parts of food protein His figures likewise demonstrate the superior value of meat fish and milk proteins in contrast to vegetable proteins A possible exception is the combined proteins of the soy bean which Daniels and Nichols (1917) found to compare favorably with milk Mitchell has used still another method based on the ability of a young animal to retain dietary protein He obtained for milk protein a value of 85 per cent for beef heart kidney and liver about 75 per cent for potato protein 67 per cent McCollum Simmonds and Parsons (1921) likewise found that combinations of milk protein and cereal and legume protein fail to show as high biological values as can be demonstrated for kidney liver and muscle protein combined with those of certain cereals

Hartwell (1917) further showed that the proteins of oatmeal, though good for growth in rats were inadequate for gestation and lactation Supplementary additions of casein or egg albumin, however, improved the diet

The behavior of gelatin is somewhat anomalous When gelatin is fed it is found to have a limited usefulness Bischoff and Voit (Voit, 1881) showed that even in large quantities it was always completely burned but with some of the body protein in addition In short, gelatin cannot build new tissue though it may spare body protein somewhat The fact that gelatin lacks tyrosine and tryptophane (see Table I) doubtless explains its limited utility In the diabetic mammal however it yields the same amount of sugar as does meat protein Abderhalden showed moreover that when the missing amino-acids are added gelatin behaves like ordinary protein

The Essential Amino Acids

Seuffert and Marks (1925) fed a dog a mixture of amino-acids including asparagin leucine, tyrosine tryptophane glutamic acid and alanine in addition to a non protein diet The mixture was found to spare body protein somewhat but not until cystine and lysine were added would this mixture produce nitrogen equilibrium Furthermore Abderhalden (1912) demonstrated in a dog not merely nitrogen equilibrium but also nitrogen retention when the diet contained a mixture of pure amino-acids simulating the composition of ox muscle Peptones and amino-acid mixtures are therefore nutritional equivalents of protein They are not satisfactory substitutes, however, because they often produce diarrhea

Many attempts have been made to reduce the amino-acids in the diet of experimental animals to a select few Hopkins (1916), for example found that rats did fairly well on a diet containing as nitrogenous foodstuff only the following five amino-acids tryptophane cystine histidine lysine and tyrosine This diet however would not support growth to the point of normal maturity and reproduction At the present time most biochemists accept the view that mammals are almost completely dependent upon the vegetable kingdom for their amino-acids The only proved exception is glycine which is manufactured by mammals in large quantities to form hippuric acid after the ingestion of benzoic acid as Magnus Levy (1905) showed

As to the synthesis of other amino-acids by mammals a large and conflicting literature exists That the more complex aromatic amino-acids are not synthesized in mammals however is demonstrated by experiments in which gelatin is fed to such animals Gelatin is deficient in tryptophane and in cystine and nitrogen equilibrium can be established only when these amino-acids are added to the diet containing gelatin (Kauffmann 1905) Furthermore Henriques

(1907-8) hydrolized protein and found that the hydrolysate maintained the organism in nitrogen equilibrium provided that a pronounced tryptophane reaction could still be obtained When this was lost the mixture of amino-acids was inadequate

The problem is further complicated by the presence of intestinal flora because lower organisms are known to synthesize protein from sugar and some simple source of nitrogen The various aliphatic aromatic and heterocyclic amino-acids may all be formed by yeasts and by some bacteria from carbohydrate and ammonium salts In fact Henriques and Andersen (1914) used such bacterial masses as the source of the protein food in metabolism experiments This synthetic process to be sure is in essence the reverse of deamination

These complicating circumstances and conflicting opinions as to which amino-acids are indispensable prevent a final statement being made To date the only amino-acids which have been proved indispensable beyond a doubt are histidine tryptophane and cystine (Mitchell and Hamilton 19 9) In addition lysine is needed for growth Lightbody and Kenyon (19 8) have refuted the indispensability of tyrosine Likewise Mitchell and Hamilton have doubted that proline is absolutely necessary Bunney and Rose (1928) believe that arginine and probably glutamic and aspartic acids are not indispensable constituents of food Obviously much more experimental work must be done before the question is settled

DIETS HIGH AND LOW IN PROTEIN

In a large clinic the physician is able to delegate to experienced dietitians the regulation of protein intake When treating patients suffering from chronic disease however most practicing physicians are called upon for more detailed supervision of the diet in the home or in a community hospital Under these circumstances certain fundamental devices are useful to be borne in mind as a background for the actual prescription of a practical diet Effective and safe dietary therapy must be constructive It is not sufficient to issue negative instructions to patients don t eat this or omit such and such Without explicit instructions protein deficiency malnutrition and even dwarfism in children may result

In planning a diet whether for a normal individual or for one with disease it is important from the standpoint of protein minerals and vitamins to start with a foundation of milk fruit vegetables and eggs This daily foundation diet we shall designate as F In the case of an adult it should include at least one half to one pint (480 c c) of milk or one ounce (30 gm) of cheese (not cottage cheese) one fruit preferably raw two vegetables other than potato and three or four eggs a week In the case of a child the milk should be in

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in the American diet i e calcium and vitamins A C and the so-called G To these basic requirements may be added nutriment of two categories The first group which we shall call group C consists in breadstuffs cereals sweets and fats sufficient to satisfy the individual s caloric requirement and to maintain

TABLE XIV

GROUP C HIGH CALORIC LOW PROTEIN FOODS

	Amount	Carbohydrate gm	Protein gm	Fat gm	Calories
Sugar	3 lumps	15			60
Jam Jelly Honey Molasses Syrup	1 tbsp	20			80
Jello	1 serving	18	1		75
Prunes Bananas Dates	av serv	25	1		100
Grapejuice	4 oz	22			90
Crackers (Uneedas)	3	15	1	1	0
Butter	1 tbsp			12	110
Mayonnaise French dressing	1 tbsp			11	100
Heavy cream	2 tbsp	1	1	12	115
Avocado	one half	7	2	20	215
Bacon	3 thin slices		3	10	100
Nuts	½ oz	2	3	10	110
Olives	1 large	1		3	30
Candy	3 oz				100

weight It will be noted that these foods add little protein Groups F plus C therefore together constitute a low protein diet In group P on the other hand are meats fish and additional milk to supply protein as required Just as the amount of group C foods may be varied to adjust total calories so the amount of group P foods may be altered to adjust total protein

By way of illustration the diet (group F) shown in Table XIII on the preceding page is for an adult weighing 70 kilograms It contains common foods arranged according to customary American habits of eating For convenience figures are based on families of foods with approximately equal energy values Main luncheon dishes may vary from sandwiches in a workman s dinner pail to the housewife s left overs from yesterday s dinner It should be noted that common American desserts excepting fruit are high in carbohydrate and fat but low in protein The problem of salt and fluid intake will be neglected in this short summary

This foundation diet (Table XIII) will be found to yield only three fifths

creased to one quart daily to ensure a sufficient amount of high quality protein and minerals to meet the demands of growth

These fundamentals have been called protective foods" by McCollum and Simmonds (19 9) because they provide the essentials most likely to be lacking

TABLE XIII

Foundation Diet Group F For ,o kg Adult
Containing protective foods essential for normal nutrition

Breakfast	Amount (approximate)	Protein gm	Calories
*Fruit raw	av portion	1	30-1 5
Cereal	⅔ cup	3	70
Light cream	3 oz	3	150
Sugar	2 tsp		40
*Egg	1	6	,0
Toast (muffin or roll)	1 slice	3	,0
Butter	1 square		80
Coffee			
Medium cream	1 oz		60
Sugar	1 tsp		20
Lunch or Supper			
Potato Bread Rice Macaroni etc (for sandwich or usual left-over dish)		2-6	140
Salad and		1	0-60
Dressing	1 tbsp		100-150
Milk	6 oz	6	120
Fruit canned	½ cup	1	100-200
Sugar cookies	two 3¹ in diam		150
Dinner			
*Vegetable	½ cup	2	20-60
Potato	1 medium	3	120
*Salad or second vegetable	½ cup	2	20-60
Bread whole grain*	1 slice	3	,0
Butter	2 squares		160
Ice cream	2 heaping tbsp	3	210
Coffee			
*Medium cream	1 oz	1	60
Sugar	1 tsp	1	20
Total		41-45	1900-2 65

*These items are essential Those *not* starred may be decreased with a substitution of high caloric food from group C All measurements are level

Thus three P_1 servings plus three P_2 servings would bring the diet up to about 125 grams of protein daily Egg white slightly cooked for maximum absorption may be incorporated in other foods and in beverages without adding bulk With the very high protein diets it may be important to change the texture of food by sieving or chopping so that it will require little effort in chewing and ingesting

The scheme here presented is of course merely illustrative of the sort of method by which alteration in diet may be made conveniently if disease progresses The detailed protein contents and caloric values here given were arranged by Mrs Beula Marble Further information may be had from the League of Nations Publication (1935) as cited

V

THE PROTEINS IN DISEASE

Disturbances Primarily Due to Abnormal Protein Metabolism

A number of disturbances are recognized which have to do with the assimilation or metabolism of proteins which arise outside of the human body It is interesting that these disturbances probably are secondary to some defect in the physiological behavior of the individuals involved because they are not of universal occurrence Certain it is that many individuals can eat with impunity large amounts of proteins formed either by animals or by vegetables other than simple microorganisms but not all proteins can be safely ingested

Intoxications and Idiosyncrasies

In the seeds of Abrus precatorius occurs the protein abrin which is highly toxic So also is ricin, which is formed in the castor oil bean To be sure it seems likely that these are conjugated proteins the toxicity of which resides in a prosthetic group (Kossel 1928) as already explained Nevertheless the toxicity cannot be destroyed without decomposing the proteins Ehrlich (1892) was able to immunize animals against both of these proteins

On the other hand when certain products of protein origin are administered parenterally a considerable number of apparently normal men react unfavorably In some instances it is possible that the untoward effect is due not to protein per se but to associated substances Thus heterologous sera usually are harmless when eaten but toxic when injected in considerable amounts The intravenous dose which may be tolerated varies not only with individuals but also with the source of the protein The serum of eels for example is toxic to mammals in minute doses when injected whereas horse serum is relatively

gram of protein per kilogram of body weight If it seems desirable to restrict protein intake to this extent there remains only the caloric requirement to be made up by adding foods in group C, if necessary to complete the total diet (see Table XIV) Bacon however, must be avoided if salt is to be restricted

TABLE XV

GROUP P PROTEIN FOOD — AVERAGE SERVINGS

P_1 High protein Foods	Amount approximate	Protein gm
Beef		
Liver	3 oz cooked	
Veal	or portion	
Lamb lean	the size of	
Ham	a package of	25
Pork chops	cigarettes	
Fish lean		
Sweetbreads		
Cheese cottage		
P_2 Moderate protein Food		
Milk	6 oz	
Buttermilk	6 oz	
Beans (dried)	½ cup cooked	
Peas	½ cup cooked	
Cheese American	1 in square	6
Egg	one	
Egg whites	two	
Oysters	½ cup or 7 med	
Bread	2 slices	
Nuts	1 oz	

*Incomplete proteins may be used only in conjunction with animal proteins

Usually it will be found desirable to add more protein than the Group F foods supply and to this end foods from Group P are added (see Table XV) These have been subdivided into two subgroups each average portion from P_1 will add 25 grams of protein whereas each portion from P_2 will furnish only 6 grams of protein By this device a wide range of protein intake may be arranged readily The average normal individual would take the foundation diet (F) plus a serving of animal protein (P_1) at dinner and a small amount of meat, or fish egg or cheese at lunch Such a diet would yield one to one and a half grams of protein per kilo of body weight

For very high protein diets i e up to 2½ grams of protein per kilo and even higher it will be found necessary to draw largely upon the group P foods

by the purified carbohydrate moiety which is practically nitrogen free In this connection it should also be remembered that the serum proteins of animals and man contain a carbohydrate group, and this may be involved in serum specific reactions

As regards the immune bodies they, too are protein in nature and have been identified with the globulin fraction of the plasma Interesting evidence of their rôle in allergic phenomena is the experiment reported by Prausnitz and Kustner (1921) in a case of idiosyncrasy to fishy food In this instance serum from the hypersensitive individual was infiltrated by hypodermic injection into the skin of a normal recipient The next day the normal recipient ate fish and shortly afterward the infiltrated area of the skin changed from a normal appearance to that of acute allergy

The nature of the precise chemical reaction involved in these allergic phenomena remains a mystery Novy and de Kruif (1917) suggested that the toxic substance is a serum globulin transformed into a tautomeric form similar to the transformation of fibrinogen into fibrin Lewis (1927) and other investigators have hypothecated the production of an H substance similar to or identical with histamine Among the clinical phenomena which bear upon this question is the precipitation of the attack of bronchial asthma with histamine in asthmatic individuals

It is still undecided to what extent tissue proteins as distinguished from blood proteins are involved in anaphylaxis and related responses Besredka (1925) long maintained the existence of a localized tissue immunity Sensitivity to uveal protein has been discussed by A C Woods (1936) as an important factor in the so-called sympathetic ophthalmia Somewhat analogous are the auto-hemolysins demonstrated by Donath and Landsteiner (1925) in cases of paroxysmal hemoglobinemia Of course it is clear that tissues remain allergic to foreign protein long after antibodies have disappeared from the circulating blood In recent years this fact has led to the application of cutaneous reactions to the nucleoproteins of streptocci tubercle bacillus echinococcus trichinella and other parasites causing disease That allergic responses on the part of renal tissue may result in sev re kidney insufficiency was pointed out by Longcope and Rackemann (1917) and recently confirmed experimentally in animals by Farr and Smadel (1937) Libman (Libman and Sacks 19 4) too has voiced the opinion of many clinicians that allergy may account for the so called rheumatic nephritis and other rheumatic lesions

It was believed formerly that bacteria could form poisons by a simple chemical modification of proteins Thus by decarboxylation i e splitting off CO_2 from amino-acids amines might be formed known as the ptomaines Putrescine and cadaverine are indeed definite chemical substances isolated under such conditions The evidence is now overwhelming however that ptomaine

harmless Large doses of horse serum may produce the well known "serum sickness", and the larger the dose as Weaver (1909) showed or the cruder the serum, the more marked the response The six to ten day interval, which elapses between the injection and the onset of symptoms, suggests that an allergic state is being produced in the individual, who subsequently reacts anaphylactically to such foreign protein as remains undestroyed

The split products of proteins may also produce disease Vaughan (1913) found that pathogenic bacteria produce toxins, which are either themselves protein or very intimately associated with proteins Minute doses were fatal to guinea pigs when injected intraperitoneally and were toxic on inhalation by the experimenter Even more striking is the toxic effect which can be produced by the injection of albumoses into animals Even though obtained by the splitting of non toxic proteins like edestin casein and egg albumin these protein intermediates produce a "peptone shock" on injection as Whipple and Cooke (1917) showed Whipple and Van Slyke (1918) found that dogs, so treated digested their own tissues at such a rate that the blood urea rose rapidly as if they were assimilating large meals of meat

In general it may be said that normal men rarely are made ill by protein from exogenous sources under the usual conditions of life Certain individuals, however, are intensely poisoned by the injection, ingestion or even inhalation of minute amounts of protein which are harmless to others Since Dunbar (1905) showed that hay fever was specific and Weichhardt (1906) that it is due to the proteins of pollen an extensive literature has accumulated This subject is discussed at length in Vol II, Chapt VI-A and it suffices for the moment merely to emphasize the protein character of the substances involved A majority of the antigens capable of sensitizing animals and man have proved to be protein in nature An interesting example of this fact is the immunity to plastein shown by Herrmann and Chain (1912) They found that, whereas peptone or albumose produced no immune reaction, nevertheless the artificial protein produced therefrom behaved like a typical antigen Landsteiner and Jacobs (1936) in recent years have investigated those cases of drug allergy and related phenomena in which the allergy is patently not provoked by a protein Even in these instances the discrepancy may be more apparent than real because Landsteiner's evidence suggests that the substances in question combine with body protein spontaneously to form as it were, a conjugated protein

As regards the nature of antigens Avery and Heidelberger (1925) have shown in the case of pneumoccocus antigens that they contain a nucleoprotein fraction which is specific for the species and a carbohydrate group which is specific for the particular strain of pneumococcus involved It is highly significant that precipitin reactions and even skin reactions with immune bodies may be elicited

corn, beans and peas are digested and absorbed with practically the same completeness as meat proteins if they are freed of cellulose coating and finely ground before ingestion The frequent use of a meat grinder or seprosieve by the edentulous therefore is indicated In infants the formation of large and tough casein curds by the action of gastric rennin upon mixtures containing cows milk may be important as is discussed elsewhere

Indigestible solids are particularly undesirable because they act to stimulate peristalsis while simultaneously retarding the normal absorption of digested food Among such substances described by Mendel and Lewis (1913-4) are vaseline or paraffin filter paper, ground cork and agar It is obvious that in cases of severely impaired nutrition the injudicious use of roughage must be avoided The unsatisfactory results of adding ground wood or other cellulose to bread were experienced in central Europe during the last war

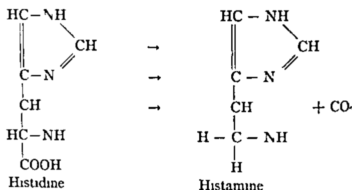
The degree of wetting also is an important and an obvious purpose of mastication Indeed meats are digested even if not finely ground probably because the digestive ferments can diffuse into their moist colloids Even after ordinary cooking most meats contain more than 50 per cent of water On the other hand large pieces of meat fried brown in fat may be covered by a layer of lipoid which the gastric juices cannot readily dissolve or penetrate Hawk (1919) found however that ordinary frying does not greatly affect the digestion of meats presumably because chewing exposes fresh protein surfaces to the gastric juices

The only common completely indigestible protein is keratin the chief protein constituent of hair Hair balls may remain undigested for long periods in the stomachs of animals or of man

Coagulation of protein by cooking seems not to be an important factor in its digestion An important exception however is egg white which may be excreted in large part unchanged when eaten raw Indeed Mendel and Lewis caused profuse diarrheas in the dog by feeding uncooked egg albumin The failure of uncoagulated egg albumin to change to albumose in the stomach is due to a specific resistance to enzymic digestion and has been ascribed to anti enzymes

Abnormality in Gastrointestinal Function — In a subsequent section it will be pointed out that interference with the normal rate of food passage through the intestinal canal may produce profound malnutrition In short circuits produced surgically or in ulcerative lesions of the bowel the abnormally rapid passage of food through the alimentary canal may prevent complete digestion and also limit the absorption of the products of digestion Chronic obstruction of the bowel produces its deleterious effects chiefly through vomiting and nausea in so far as protein is concerned To be sure Whipple formerly attributed the collapse in acute intestinal obstruction to the absorption of toxic albumoses

poisoning is in reality due to complex bacterial toxins to which protein contributes only indirectly Among these toxins those of *B botulinus* and *B enteritidis* are the best known and are discussed elsewhere One of the most poisonous ptomaines is histamine, which is known to occur in the intestine, and which is produced directly from the amino acid, histidine, by decarboxylation



Histidine Histamine

This substance has been studied extensively by Sir Thomas Lewis and his collaborators (1927) It produces many effects in the body among them cutaneous wheals stimulation of smooth muscle, depression of blood pressure and stimulation of acid secretion in the stomach Dale and Laidlaw (1919) found that when injected intravenously it caused symptoms resembling those of traumatic shock When ingested with food however, it is not sufficiently toxic to cause serious symptoms

Abnormality in the Alimentary Canal

As pointed out in an earlier section the nitrogen of the feces normally consists chiefly of intestinal secretions and bacteria Usually digestible proteins are absorbed completely The effectiveness of digestion may however, be diminished by mechanical or chemical factors in the food itself or by mechanical or chemical abnormalities of the intestine

Physical Factors in Food —The physical state of food must be such that digestive juices can find access to the inherent protein As pointed out earlier the enzyme must combine with protein to digest it and may be prevented from so doing by purely mechanical causes Fineness of division and freedom from occlusion by indigestible substances obviously are important although over emphasized by the Fletcherizers The presence of efficient teeth is an important item in the process of mastication Daniels and Loughlin (1918) showed that finely ground peanut meal was well used whereas whole roasted peanuts might pass through the alimentary canal practically unchanged Mendel and Fine (1911–2) showed also that the proteins of wheat barley Indian

entrance into the intestine Furthermore practically all of the proteolysis must now occur in the small bowel It is easy to understand therefore why flatulence and diarrhea occur in pernicious anemia hypochromic anemia sprue and gastric cancer, and why liberal doses of hydrochloric acid may remedy the defect

The clotting of milk protein by gastric juice i e the transformation of casein into paracasein is a complicated problem It is known that acid alone will clot milk Whether rennin and pepsin are identical or different enzymes is not known definitely Molecular weight studies indicate that the paracasein is produced by splitting the casein molecule into two parts The paracasein forms an insoluble calcium compound and clots , whereas the whey albumose remains soluble Many secondary factors affect the toughness and size of the clot or curd such as preliminary boiling the presence of salts and the source of the milk In the absence of both acid and pepsin or rennin the digestion of milk must occur largely in the intestine

In the duodenum the acid gastric contents meets the alkaline pancreatic juice The resultant mixture usually remains acid in the duodenum but gradually becomes more alkaline as it traverses the small intestine The optimum reaction for tryptic action is pH 7 8 i e slightly alkaline So effective is this pancreatic secretion that even after gastrectomy normal protein nutrition may be maintained Barker (1916) showed however that when pancreatic secretion failed protein was not adequately absorbed In pancreatic disease as much as 6 to 15 grams of nitrogen per day may be excreted in the feces as compared with 2 or 3 grams in normal individuals

In recent years two further chemical properties of the alimentary canal have assumed importance with respect to protein nutrition The first is the pernicious anemia curative substance of Castle (1936) The extrinsic component of this may not be protein itself although it is present in meat The combination of extrinsic with the intrinsic gastric factor is however absolutely essential to the normal formation of the protein hemoglobin

Another chemical derangement of the bowel is seen in the protein lack frequently encountered in the so-called deficiency states In sprue in beri beri and in pellagra protein malnutrition looms so large as to be a major factor in the disease Here inadequate dietary protein may play a rôle but many cases have diarrhea and are unable to assimilate a normal and adequate amount of protein It has also been suggested by Jones (1936) that possibly the avitaminous bowel is so altered as to its absorptive capacity that the assimilation of foodstuffs may be inefficiently performed As yet there is no definite proof of this so far as protein is concerned McLester has pointed out that the most reliable test of defective protein digestion in such conditions is the examination of the feces for undigested meat fibres creatorrhea following the test diet of A Schmidt (1908)

derived from protein but this theory has not been accepted Cannon has emphasized also the fact that emotional factors through the autonomic nervous system may provoke chronic digestive disturbance by inhibiting intestinal motility and secretion Indeed, Van Slyke, Cullen and McLean (1915) found experimentally in the actively digesting dog that the administration of anesthesia produced a complete interruption of digestive processes, as judged by studies of blood nitrogen

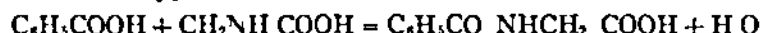
Chemical Factors in the Gastrointestinal Tract — Chemical abnormalities in the digestive tract have long been recognized as being associated with 'indigestion of various sorts The two most important chemical factors to be considered are the acidity and the activity of enzymes

The gastric juice normally is acid because of the 'free hydrochloric acid present This free acidity is due to hydrochloric acid which is not combined with either base or protein Gamble and McIver (1928) showed that the free hydrochloric acid present in gastric juice constituted only a small fraction of the total chloride At a pH value equal to 1 0 the gastric juice approaches 1/10 normal hydrochloric acid and in consequence, 100 c c of stomach contents would require approximately 100 c c of 1/10 normal sodium hydroxide solution to neutralize the free acid The usual indicator used for free acid is methyl yellow Topfer s indicator

When gastric contents are measured after fasting or when a non protein meal is given, very little difference in amount will be found between free acid and total acid When there is organic acid present, like lactic or butyric acid or when there is organic material to combine with hydrochloric acid, the difference may be great This is especially true when protein food is undergoing digestion in the stomach It was formerly stated that pepsin became inactive near the turning point of Topfer s reagent From the standpoint of digestive activity this is essentially correct although Wasteneys and Borsook (1930) have demonstrated that at this acidity pepsin shows a marked synthetic activity, i e , the reverse of digestion The free acidity of the stomach is subject to a considerable emotional or psychic variation Normally, however, it varies from about the equivalent of 1/10 normal hydrochloric acid at pH equal to 1 in pure gastric juice to 1/1000 normal hydrochloric acid at pH equal to 3 in juice which has been partially neutralized by protein food The optimal acidity for peptic action is near pH 1 8 or about midway between these two normal extremes

It is obvious that lack of acidity in the stomach would hinder digestion because pepsin even if present in large amounts, would not be activated Inasmuch as the normal gastric acid prevents the growth of organisms and in fact kills most of them except spores it follows that, when acid is low the poorly digested protein food may undergo putrefaction either before or after its

In the urine of cattle and horses is found hippuric acid a compound of benzoic acid with glycine



$$C_6H_5COOH + CH_2NH\ COOH = C_6H_5CO\ NHCH_2\ COOH + H\ O$$

Blatherwick and Long found it also in the urine of man after eating prunes and cranberries H B Lewis (1914) found that after giving hippuric acid to a man 82 per cent appeared in the urine within 3 hours Ringer (1911–12) has reported that 38 per cent of the total urinary nitrogen excreted by the fasting goat might be eliminated in the form of hippuric acid Shiple and Sherwin (1922) showed in man that the glycin nitrogen so excreted does not add to the wear and tear protein metabolism but is as it were subtracted from the urea nitrogen

In the intestine bacteria act upon tryptophane and convert it into skatol or indol Similarly from phenylalanine and tyrosine as the result of bacterial de composition arise phenol and p-cresol These substances are all conjugated with sulphuric acid in the liver and are eliminated as ethereal sulphates in the urine Indican was formerly tested for in urine as evidence of intestinal auto-intoxication but now it is generally believed to be unimportant

Disturbances in Protein Metabolism Secondary to Disease

Abnormal Protein Metabolism

Much more common than the cases showing unusual end products of me tabolism are those in which the degree or extent of protein anabolism and catabolism are interfered with The synthesis of body protein may be impaired for example not only by protein lack but also by deficiency in other dietary factors such as insufficient mineral salts as iron for blood protein and calcium for milk protein or by insufficient carbohydrate or by fat and vitamin lack In ' total diabetes with severe glycosuria protein rebuilding appears impos sible Children so afflicted failed to grow before insulin was available and soon died Similarly in cretinism growth fails to occur and therefore protein syn thesis is small although nitrogen equilibrium is maintained

Normal End Products in Abnormal Amounts —To eliminate the end products of protein catabolism is one of the chief functions of the kidney As out lined in a previous section the chief end products of protein catabolism in man are urea and ammonia Although only a small fraction of the total urinary nitrogen is contributed by other substances these may nevertheless undergo significant alterations in disease Notable among these are creatine and crea tinine which are particularly influenced by the autolysis of body tissue Al though it is not certain that these are formed directly from protein their metabolism seems to be related to that of protein and of muscle in particular

Abnormal Metabolic End Products of Protein Metabolism

In certain clinical conditions and anomalies of metabolism the natural course of protein breakdown is diverted or interfered with In acute yellow atrophy of the liver amino acids appear in increased quantity in the blood and in the urine The source of these catabolites is two fold, they arise in part from autolizing liver protein and in part from other tissues In either case their failure of deamination is due to insufficient hepatic function Because they are relatively insoluble and crystallize readily, leucine and tyrosine may be observed on simple microscopic examination of the urinary sediment in some of these patients

In chronic cirrhosis of the liver, however, ordinarily there is no unusual amount of amino acid which escapes deamination Even in the acute liver degeneration of the toxemias of pregnancy such a finding is rare In severe acute yellow atrophy, however the amino acid nitrogen in the urine may rise from the normal level of barely 2 per cent up to 16 per cent of the total nitrogen The blood amino nitrogen Stadie and Van Slyke (1920) found might rise from 8 mg per cent to 26 Such figures of course represent an extreme degeneration in which the high factor of safety in liver capacity is exceeded

In the rare anomaly of metabolism termed alkaptonuria, homogentisic acid appears in the urine as the end product of oxidation for tyrosine and phenylalanine The explanation of this phenomenon was given by Frommherz and Herrmanns They believe that one path leading to the destruction of aromatic amino-acids is closed in alkaptonuria Hence degradation stops at the stage of homogentisic acid

The alkaptonuric patient turns into homogentisic acid the non nitrogenous portion of all the tyrosine and phenylalanine which he utilizes This is true both of amino acids arising from exogenous i e food, protein and those of endogenous i e tissue origin Nevertheless these amino acids are used normally for the synthesis of cell protein in growth Likewise there is no evidence that these aromatic amino-acids are not deaminated as in normal individuals The explanation seems simply to be that after deamination these acids are oxidized to the stage of homogentisic acid but fail to be oxidized further as in the normal individual Homogentisic acid itself is colorless but on exposure to air it is oxidized to a melanin like pigment whence the term alkaptonuria, i e , dark urine

A somewhat similar disease is cystinuria a quite rare condition, in which cystine appears in increased amounts in the urine and may even form gravel or stones When such a patient is given a high protein diet the cystine output becomes greatly increased Obviously in such a patient the normal progress of oxidation to sulfate is interfered with Possibly there is a deficiency in some enzyme system peculiar to sulphides because the other amino-acids are metabolized in normal fashion

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In general urea and ammonia tend to be mutually complementary in amount Page (1935) recently has studied this point and showed that the sum of the two should be used to measure the urea cleared from the blood Under alkali therapy ammonia may nearly disappear from the urine, whereas acid producing salts may elevate it over ten times the normal value (Salter, Farquharson and Tibbetts 1933) In extreme diabetic acidosis ammonia nitrogen may rise to 5 or 6 grams a day If a low protein, high carbohydrate diet be given to normal individuals urinary urea plus ammonia falls because protein catabolism is less During rapid autolysis of body tissue, conversely, the urea plus ammonia nitrogen will rise In pneumonia (Wolf and Lambert, 1910) in typhoid fever in eclampsia and in infantile marasmus part of the urea is replaced by unidentified nitrogenous matter This "undetermined nitrogen occurs in normal urines to the extent of some 3 to 5 per cent, but in disease occasionally reaches 20 per cent of the whole

As pointed out earlier hippuric acid is formed by the conjugation of benzoic acid and glycocoll as a detoxication mechanism When it appears in the urine ordinarily it replaces the urea nitrogen

Creatine and Creatinine — Hunter (1922) has shown that these substances, like arginine, are derivatives of guanidine Normal muscles contain about 0 4 per cent creatine largely in the form of phosphocreatine according to Fiske and Subbarow (1929) On the contrary there is only about 0 004 to 0 01 per cent of creatinine in muscles Nevertheless normal adult men excrete no creatine but do excrete regularly creatinine in surprisingly constant amounts This creatinine excretion is so constant that it has been used frequently to determine whether all of the 24 hours urine has been saved The creatinine elimination is not increased by muscular work nor does the increased metabolism of body proteins in phosphorus poisoning cause an increase in creatinine Such observations as these led Shaffer (1908–9) to regard the creatinine coefficient, previously described as an index of muscular development Folin (1914) regarded it also as an index of endogenous metabolism because it was so constant in any given individual When fed or injected creatinine is excreted almost quantitatively in the urine In severe acute nephritis or in the terminal stages of chronic nephritis it usually accumulates in the blood as is discussed by Christian and O Hare Oxford Med Vol III Chapt X

Creatine is not often found in the urine of normal adult men but occurs frequently in women Rose found no relation between creatinuria and the sexual cycle Usually it is found in growing children of both sexes F G Benedict explained its presence in the urine of fasting men on the basis of the disintegration of muscle tissue In recent years Shorr Richardson and Wolff (1933) have found outbursts of creatine excretion when a sharp elevation of metabolic rate occurred in myxedema or in hyperthyroidism Here again it is

known that excess protein is eliminated under these circumstances in fact in hyperthyroidism muscle atrophy may be striking (Palmer Carson and Sloan 1928–9) Creatinuria likewise occurs in phosphorus poisoning carcinoma of the liver during involution of the liver during the muscle atrophy following nerve section and after gross injury and necrosis of muscle Muscle breakdown therefore seems to be an important cause for creatinuria Cathcart (1906–7) suggested however, that carbohydrate starvation was a chief cause of creatinuria and S R Benedict with Osterberg (1914) showed that it might be marked in degree while body protein remained constant

The amounts of creatine excreted vary considerably In males over 6 years of age the amount of urinary creatine is a rough indication of the rate of tissue destruction In myasthenia gravis small amounts of creatine frequently are found in the urine and such individuals often show a deficiency in their ability to convert creatine to creatinine

The Toxic Breakdown of Protein

In febrile infectious diseases the excretion of nitrogen tends to increase despite adequate caloric consumption This phenomenon called the toxic destruction of protein represents actual autolysis of tissue The extra nitrogen is excreted chiefly as urinary urea and ammonia (Kocher 1917) Krause (1926) also found excessive amounts of amino-acids in the urine of patients with typhoid fever and with tuberculosis accompanied by fever Various investigators have attempted with little success to combat the nitrogen loss by dietary means Shaffer and Coleman (1909) for example were able in only one of several typhoid fever patients to obtain nitrogen equilibrium even though they gave 90 calories per kilo and 1 6 gm of protein per kilo per day Similar results have been reported in paratyphoid fever (Kocher 1917) Such patients excrete about 15 gm of nitrogen daily instead of the normal 3 or 4 grams

Experimentally Whipple and Van Slyke (1918) were able to provoke a more striking but similar effect in dogs by intravenous injection of proteose Within a few hours the blood non protein nitrogen of such animals rose to a high level In fact the blood urea rose exactly as it would have risen in the course of protein digestion following a meal of meat Of course in this instance the source of the urea was not food but the almost explosively autolyzed body proteins These experiments constitute at present our best indication as to how toxic conditions lead to the destruction of body protein Of course the ultimate mechanism of the effect on individual cells remains unknown

Gastrointestinal obstruction likewise produces marked breakdown of body protein as demonstrated by Whipple and associates (Cooke Rodenbaugh and Whipple 1916) and by Haden and Orr (1927) The destruction certainly is

aggravated by the combined starvation and dehydration, and these may well be the chief causative agents Hartmann and Scott (1926) have shown that the excessive nitrogen catabolism can be ameliorated by the administration of salt solution Similarly Walters, Kilgore and Bollman (1926) obtained azotemia in dogs with duodenal fistulæ and relieved the condition with isotonic sodium chloride solution In most of these various observations it was found that the urine contained in highly concentrated solution considerably more than the normal amount of nitrogenous catabolites Rabinowitch (1921) has suggested that in clinical cases of peritonitis or in surgical abdominal conditions a persistently high blood non protein nitrogen with normal renal function indicates a poor prognosis because due to profound 'toxemia It must be remembered, however that persistent severe vomiting alone will produce azotemia, because of the resulting dehydration and starvation

Severe diarrheas also produce undue destruction of body protein for several reasons The absorption of dietary protein is impaired and Thayssen (1926) reported that analysis of the stools for nitrogen may show this He suggested this method to distinguish pancreatic disorders from sprue, because in the latter fecal nitrogen was not above normal If water loss becomes extreme as in Asiatic cholera, dehydration may become so marked that the blood becomes measurably inspissated and urine excretion is abolished (C Schmidt 1850) Under such circumstances the non protein nitrogen mounts high in the blood Finally toxic destruction of protein adds to the effect of nitrogen retention

Plasma Proteins in Disease

In recent years it has become increasingly common in the clinic to investigate the concentration of protein in the blood plasma In this way it has been possible to apply fundamental concepts of circulatory hydrodynamics to the problem of edema in the individual case Likewise it has been possible to follow in a roughly quantitative way the progress of patients suffering from malnutrition or disturbed water balance

Severe loss of fluid to the point of marked dehydration will lead to high plasma protein concentration Thus Gamble and Ross (1925) found that the vomiting which followed high intestinal obstruction in animals led to values of plasma protein of 10 grams per cent In man complete pyloric stenosis or obstruction may have this effect Even higher values, e g 11 per cent, were reported by C Schmidt (1850) in severe epidemic cholera with very copious diarrhea Frequently such elevations disappear, as the disease becomes prolonged because nutrition is interfered with In consequence the protein reserves of the patient suffer a depletion which becomes demonstrable despite

the temporary dehydration The dominant effect is then the same as that demonstrated in rats by Frisch Mendel and Peters (19 0) as a result of prolonged low protein diets i e the development of edema The same effect also is a well known consequence of famine (Mayer, 19 0) or wasting diseases (Bruckman and Peters 1930)

Such individuals tend to become edematous as the plasma protein approaches 5 5 grams per cent As seen in Fig 5 on an earlier page there is a rather sharp tran ition from non-edematous to edematous individuals at this plasma concentration which corresponds usually to a plasma specific gravity of 1 023 Both values are of course, functions of the oncotic pressure which may be calculated from Govaerts equivalents Govaerts (1926) found that the oncotic pressure in millimeters of mercury is approximately the sum of 5 5 × grams per cent of albumin plus 1 4 × grams per cent of globulin (see Fig 12 on a later page) It is possible that some day our clinical records will express this plasma oncotic pressure directly It is interesting that usually the globulin concentration in plasma tends to hold nearly constant in hypoproteinemia whereas the drop in the albumin fraction is marked as Wies and Peters (1937) have pointed out Recovery to normal levels occurs chiefly by rise of albumin in the blood Of course these are exceptions to this general trend

Edema in Relation to Plasma Proteins

In a previous section it was pointed out that normally there is an equilibrium between the circulatory hydrostatic pressure in the blood capillary and the osmotic pressure of the pla ma protein (see Fig 6) In consequence the flow of liquid A from the proximal part of the vessel is approximately equal to the flow of liquid B back into the distal portion of the vessel (This concept of course neglects the lymphatic circulation) Under abnormal circumstances however it may happen that the hydrostatic pressure overbalances the osmotic pressure of the plasma proteins (see Fig 10) In such cases Flow A out from the vessel will be greater than Flow B back into the blood and fluid will therefore collect in the tissues Edema may be conceived of as arising in this manner in two general cases As shown in Fig 10 circulatory stasis may cause the initial intracapillary hydrostatic pressure to increase above the normal pressure i e above 30 mm of mercury In consequence the balance of pressures will be upset along the length of the capillary in favor of outward filtration Or on the contrary as shown in Fig 11 the hydrostatic pres ure may be normal but the protein osmotic pressure unusually low Here again the fluid balance will be upset and edema will occur It is this latter case which concerns us most in studying the relation of edema to plasma oncotic pressure In this instance the net filtration pressure forcing fluid out through the capillary

wall is abnormal because the osmotic resistance to normal blood pressure is low. Therefore Flow A″ will exceed Flow B″, as shown in Fig. 11.

This concept of edema has been developed by Schade, Govaerts and others on the basis of Starling's classical experiments on capillary function. Although

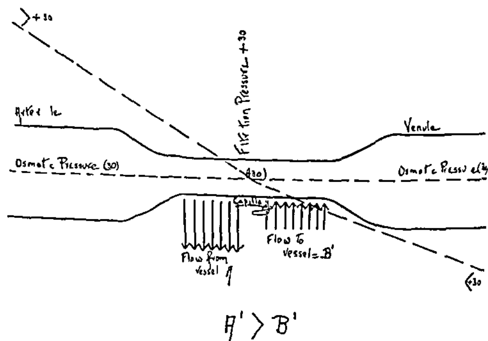


FIG. 10. In this diagram is represented the effect of increased capillary pressure as in circulatory stasis combined with normal plasma colloid pressure. The net increase in filtration pressure causes more fluid to be squeezed out than is sucked back into the capillary. From Christian (1936).

subject to several important reservations and refinements it probably will remain a useful key to our understanding of fluid balance in tissues.

It should be noted that plasma protein is merely one important factor in the development of edema. Ellis (1933) showed for example that in cardiac patients with chronic mild edema a rather small increase in plasma protein produced by a suitable diet might cause the edema to disappear. Likewise Widal and Lemierre (1903) years ago observed that increasing the salt content of the diet might precipitate recurrent edema in the chronic nephritic patient. This hydropigenous effect of sodium chloride remains as yet a mystery, because the salt in solution should penetrate capillary walls readily from either side. The effect of salt is particularly important at the critical values of 5.5 per cent for total protein or 2.5 per cent for albumin. Edema may occur clinically, of course, without lowering of plasma protein. Thus the initial edema of acute

hemorrhagic nephritis need not be accompanied by a fall in plasma protein, although a fall in plasma albumin ordinarily is found if the edema persists Furthermore often in cardiac edema there is no fall in plasma protein

Hitherto much stress has been laid upon the globulin content and the albu

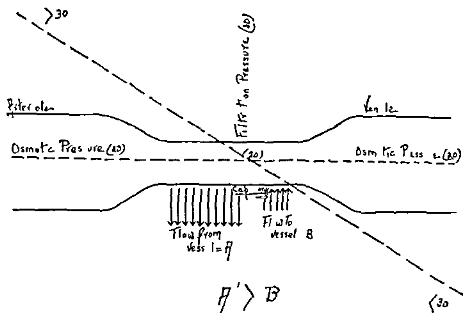


Fig 11 In this diagram is shown the effect of lowered plasma colloid pressure combined with normal capillary pressure The net filtration pressure is greater than normal and in consequence more fluid flows from the capillary than is reabsorbed From Christian (1936)

min globulin ratio Actually however plasma globulin may remain normal or increase slightly when the protein falls The effect is minimal however because Govaerts (1927) has shown that globulin is only one fourth as important in oncotic pressure as albumin (see Fig 12) Salvesen (1926–7) has shown that in rare cases a rise in globulin may partially compensate for a fall in albumin and so prevent edema High globulin is apt to be present in infection (Rowe 1915–6) as seen in Fig 15 on a later page and in such conditions as multiple myeloma However the fall in total plasma protein ordinarily is proportional to the fall in albumin Inversion of the albumin globulin ratio therefore ordinarily means that albumin has fallen

Wies and Peters (1937) studied the osmotic pressure of proteins in whole serum and surveyed the extant literature on this subject They corrected their measurements for the base bound by protein Donnan s effect and for the volume occupied by the protein They found that the colloid osmotic pressure

of the serum was not exactly proportional to the concentration of serum protei Nevertheless a first approximation showed that the colloid osmotic pressure of the protein increased by about 39 mm of water for each gram per cent of protein The actual value observed depended somewhat upon the technique

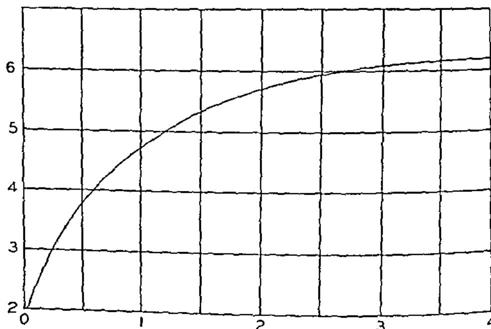


FIG 12 The ordinates represent the oncotic pressure per 1 gram per cent. of serum proteins expressed in centimeters of water The abscissæ represent the A/G ratio After Govaerts (1927 p 361) Note that above a ratio of 2 0 there is little gain in oncotic pressure per gram per cent of protein

employed The use of total protein as the sole guide to calculating osmotic pressure was not quite as exact as the use of separate values for the respective albumin and globulin concentrations These authors found that a gram of globulin had only about two-fifths the effect produced by a gram of albumin They also pointed out that, in general ' sera with high protein contain excessive proportions of globulin while those with low protein are particularly deficient in albumin The coefficients found were of the same order of magnitude as those derived by similar methods by Govaerts (19 7) and by von Farkas (1926) The coefficients however were not proportional to the generally accepted molecular weights of albumin and globulin, the coefficient for globulin was smaller and that for albumin proportionately greater than the theoretical values On the whole their data indicated that for clinical purposes it was legitimate to compute colloid osmotic pressure *from determinations of* albumin and globulin

In chronic Bright's disease certain characteristics of plasma protein may be noted depending upon the stage of the disease and the type of renal lesion (See Table XVI) The patient's condition at this juncture is dependent largely

TABLE XVI

GRAMS OF PROTEIN PER 100 C C OF PLASMA IN NORMAL SUBJECTS AND IN DIFFERENT TYPES OF NEPHRITIS

Data of Linder Lundsgaard and Van Slyke from Peters and Van Slyke (1931 p 678)

Protein		Condition of Subject				
		Normal	Nephrosis acute and chronic	Glomerulonephritis nephrotic type chronic	Glomerulonephritis vascular type chronic	Nephrosclerosis
Albumin	Max	4 9	2 6	4 1	3 9	4 6
	Min	3 4	0 6	1 6	2 4	3 4
Globulin including fibrinogen	Max	2 9	3 6	3 8	3 3	3 4
	Min	2 3	2 2	1 5	2 3	2 5
Total proteins	Max	7 5	6 7	7 8†	7 1	7 5
	Min	5 6	3 6	3 7	5 4	6 3
A/G ratio	Max	2 0	1 0	2 0‡	1 3	1 9
	Min	1 4	0 2	0 6	0 8	1 2

Maximum in edematous cases 2 6 per cent albumin
†Maximum in edematous cases 5 4
‡Maximum in edematous cases 1 3 A/G ratio

upon two additional factors namely the degree of malnutrition and the extent of proteinuria Anorexia digestive disturbances and low protein dietaries contribute toward the malnutrition Proteinuria amounting to 15 grams daily is not uncommon and without regeneration of new protein this would exhaust the plasma protein in about a week's time according to Linder Lundsgaard Van Slyke and Stillman (1924) The factors controlling regeneration of protein however are not understood and surprisingly sudden falls in plasma concentration may occur without obvious explanation In general most patients will show edema when the albumin is 2 per cent whereas in most patients with albumin at 3 per cent edema will be absent An increase in ingested protein may decrease edema particularly if urinary albumin decreases In the terminal stage albumin tends to rise as hypertension and hyposthenuria with azotemia develop Vomiting and oliguria may complicate the picture If anorexia persists malnutrition will tend to lower plasma protein

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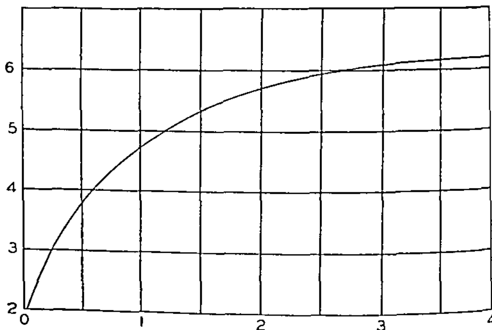


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mental hepatectomy in animals (McMaster and Drury 1929) In cirrhosis with ascites however low protein values are not invariable and it is the albumin fraction which is notably reduced often accompanied by normal or somewhat increased globulin

Proteins of Pathological Fluids in Tissues and Body Cavities

Pathological Body Fluids

If as is assumed the capillary wall tends to hold back colloidal molecules there should be very little protein in tissue fluid It is very difficult to obtain normal tissue fluid for analysis but in the edematous type of nephritis and in cardiac decompensation analyses of edema fluids (Salvesen and Linder 1923) do show 0 35 per cent of protein or less In these types of edema some damage to capillary wall probably is present In other conditions however in which there is presumably more damage to the capillary wall considerably higher values are obtained These conditions include angioneurotic edema (Govaerts 1928 b) poisoning with uranium nitrate (Govaerts 1928 a) and with paraphenylenediamine (Tainter and Hanzlick 1924–5) and purulent exudates The fluid of angioneurotic edema contains a normal proportion of globulin and even traces of fibrinogen as would be expected from an altered permeability of the capillary walls Thoracic duct lymph contains normally about two-thirds as much protein as blood serum (Arnold and Mendel 1927) a fact as yet not completely explained Normal spinal fluid is nearly free from protein under 0 08 per cent , but acute and chronic inflammation of the meninges to a less degree myxedema results in an elevated protein content (Hewitt 19 ,)

The Protein Content of Edema Fluid — It is now generally accepted that in the normal mammal blood capillaries throughout the body leak varying amounts of protein In consequence tissue fluid contains measurable amounts of the plasma proteins Field and Drinker (1931 a) pointed out that this extravascular protein normally returns to the blood vessels by the lymphatic route Subsequently Drinker Field and Homans (1934) produced edema and elephantiasis in dogs by gradual obliteration of the lymphatics in the hind legs Repeated examination of this edema fluid showed progressive increase in protein concentration up to 4 or 5 per cent as obstruction became complete At this last stage the albumin globulin ratio was only slightly higher than in blood The picture is complicated as it is in human cases of lymphedema by repeated bouts of infection with fever During these periods of inflammation there is a further increase in the protein content of the fluid above 3 per cent and large numbers of cells appear in the lymph In consequence of accumulating cells and protein gradual fibrosis sets in

It is evident that protein feeding may be an important therapeutic measure when plasma protein is low and especially when proteinuria is prolonged and marked. Even in Bright's disease, as both Epstein (1917) and Maclean (1924) demonstrated, patients with hypoproteinuria may require more dietary protein than needed by the normal individual. Such treatment may not only relieve edema but may also counteract the general wasting of the tissues from which such patients suffer. It is difficult in practice to increase protein intake much beyond 120 grams daily, and the poor appetite which usually accompanies the more severe nephritis may and usually does restrict this amount and properly so. With nitrogen retention present, as shown by increased non protein or urea nitrogen in the blood, protein feeding needs to be limited to prevent a further increase in non protein nitrogen, which in itself seems harmful.

Other chronic diseases may lead to low plasma protein through malnutrition. The possible appearance of edema, however, is complicated by other factors. Thus in heart failure hypoproteinemia may bear no relation to the water balance of the patient. In diabetes too, acidosis may stave off edema despite severe malnutrition. Indeed high plasma protein concentration may be found, even though malnutrition is evident, when dehydration occurs. Gastrointestinal disturbances, especially those of cholera infantum and Asiatic cholera, frequently lead to high values (Marriott, 1923). The severe vomiting of early pregnancy (Plass and Bogert, 1924) may produce the same result. Myxedema also (Deusch, 1920) causes a moderate elevation of plasma protein.

Increase in the globulin, and of fibrinogen in particular, is common in conditions that produce destruction or inflammation (Foster and Whipple, 1922). Multiple myeloma, kala azar and carcinomatosis also show this effect. It has been observed (Wintrobe and Buell, 1933) that the degree of Bence Jones proteinuria may be slight despite a high globulin content of the blood. Sia and Wu (1921) have shown that the high globulin of kala azar may be used as the basis for a diagnostic test. In schistosomiasis japonicum high globulin likewise is found. The precipitate with mercuric chloride described in the Takata Ara test probably is due simply to high globulin (Kirk, 1936).

Low fibrinogen, on the other hand, is common in severe anemias and in disease characterized by blood destruction. Among these are primary anemia, leukemia, hemolytic jaundice and paroxysmal hemoglobinuria (McLester, Davidson and Frazier, 1925). This is but one factor contributing to the presence of edema in anemias.

In liver disease Foster and Whipple (1922) have pointed out that two opposing tendencies may be involved: first, the presence of inflammation may elevate fibrinogen, and second, severe liver damage may limit the formation of fibrinogen. In acute yellow atrophy and chloroform or phosphorous poisoning fibrinogen invariably is reduced (Gram, 1921). The same is true of experi

Kirk (1930) showed that when the blood protein of dogs was reduced by plasmapheresis edema could be detected when the blood protein reached 4 per cent or possibly a little lower In a similar manner Field and Drinker (1931 b) reduced the blood protein of anæsthetized dogs from normal to between 3 and 4 per cent in a single day, as shown in Fig 13 The lymph from subcutaneous lymphatics under these circumstances contained about 1 0 per cent protein In contrast to this high value Leiter found less than 0 25 per cent and sometimes as little as 0 1 per cent protein in the subcutaneous edema fluid of his animals Shelburne and Egloff (1931) likewise reported only 0 13 to 0 19 per cent protein in edema fluid similarly but more slowly obtained. The discrepancy is explained by Drinker and Field (1933 p 148) as due to the acute drop in plasma protein which they produced It is known that animals subjected to plasmapheresis occasionally develop glomerular changes in the kidney, due apparently to a steady loss of protein through the glomeruli It seems possible that in acute plasmapheresis capillaries all over the body experience change, becoming temporarily more permeable to protein" Subsequently as Weech and Ling found (1931) this derangement may disappear

Protein in Inflammatory Fluids — In inflammation the blood capillaries dilate, and their permeability so increases that blood plasma may escape In such cases Lassar (1877) found an increased flow of lymph and a great increase in the total dissolved solids Field Drinker and White (1932) found this flow of lymph could be produced by applying heat to such a degree as would cause inflammation The first change noted was a rise in venous pressure of 15 cm of water at 50° C Between 50° and 60° C however the venous pressure rose to a height of 44 cm i e 27 cm above normal Meantime lymph pressure continued to rise and reached pressures as high as 120 cm of water Interestingly enough the inflammatory lymph so poured out contained as much as 5 5 per cent protein This finding is in harmony with the observation of Hudack and McMaster (1932) that very trifling injuries will cause lymph capillaries to leak dyes with ease after subcutaneous injection of the dye Thus may be explained the easy removal via the lymphatics of exudate containing protein

Even normal lymph wherever collected contains enough fibrinogen and prothrombin so that it invariably clots The increased permeability of the capillaries in an area of inflammation leads to a further concentration of coagulable material Drinker and Field (1933 p 168) consider that this fact has an important bearing upon the phenomenon of local inflammation in tissues as well as upon exudates into serous cavities In local inflammation the local lymphatic capillaries contain a tissue fluid which is essentially a gel rather than a simple solution and this gel easily clots and produces thrombosis of the local lymphatic channels

In the serous cavities previous inflammation tends to check absorption of

Analysis of fluid from human cases, though not plentiful, are in accord with the values found in experimental animals In fluid from the skin in tropical elephantiasis Desjardins (1854) found 4 3 per cent protein and Dahnhardt in 1866, found 5 4 per cent in elephantiasis occurring after erysipelas Vecchi

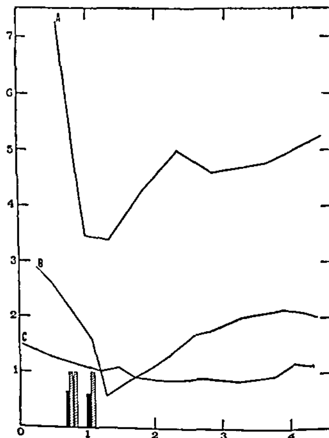


FIG 13 The effect of plasmapheresis on the protein content of blood thoracic duct lymph and cervical lymph Ordinates per cent of protein abscissæ time in hours A blood serum B thoracic duct lymph C cervical lymph Solid black portions represent amount of blood withdrawn cross-hatched portions represent volume of cells suspended in salt solution re injected (From 0 to 1 on ordinates 1000 c c) From Field and Drinker (1931 b p 383)

(1912) found in idiopathic hydrocele fluid protein values ranging from 3 0 to 9 1 per cent In one of four human cases studied by Drinker Field Heim and Leigh (1934) the total protein of edema fluid was 2 9 per cent as compared with 7 3 per cent in plasma the albumin was 2 0 per cent as against 4 0 per cent in the plasma

Lymph Flow with Lowered Plasma Proteins — Leiter (1930) and Barker and

Zuntz and Loewy (1918) found that under the exigencies of war privation the total caloric and nitrogen expenditure gradually declined. Eventually however Loewy's urinary nitrogen and basal metabolism rose above the normal

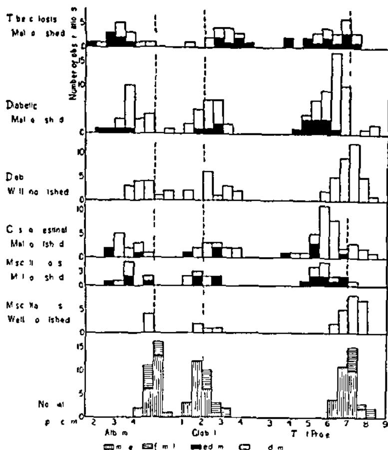


Fig 15 The relation of serum proteins to malnutrition and malnutrition edema From Buckman D Esopo and Peters (1930 p 580) The broken lines indicate the average value obtained from normal subjects Note that the columns represent the incidence of a certain analytical value In malnutrition albumin is below average whereas globulin is not correlated with the nutritional state In tuberculo is however globulin is often above average Note the correlation of edema with low serum albumin

level This paradoxical state presumably represented the state in which body proteins were disintegrated in order to obtain for the heart and other indispensable tissues certain essential amino-acids Paradoxical too is the fall in

nitrogen balance urinary nitrogen excretion gradually diminishes, and a new equilibrium may be established at a low level If the diet is high in calories despite its low protein content, such loss as may occur before the new nitrogen equilibrium is attained need not be extreme Nevertheless the individual is in

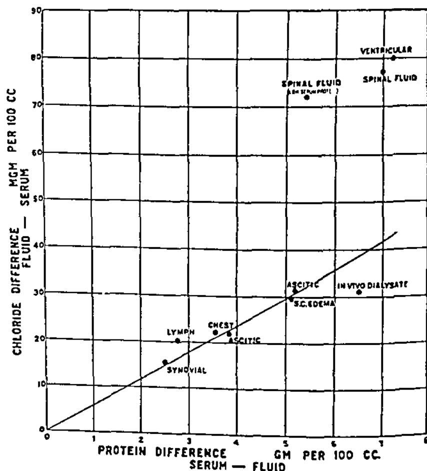


Fig 14 The relationship between the average differences in the chloride concentrations of certain body fluids and serum as compared with the average differences in protein concentration From Gilligan Volk and Blumgart (1934 p 898)

reality malnourished This may be shown by increasing the protein in the diet and noting a retention of nitrogen until the tissue wastage resulting from the preceding poor diet has been restored Raising the protein content of the mixed diet will cause the malnourished patient also to gain in weight whereas increase in protein food alone, as von Hoesslin (1919) showed, does not As the protein is increased further relatively less is retained

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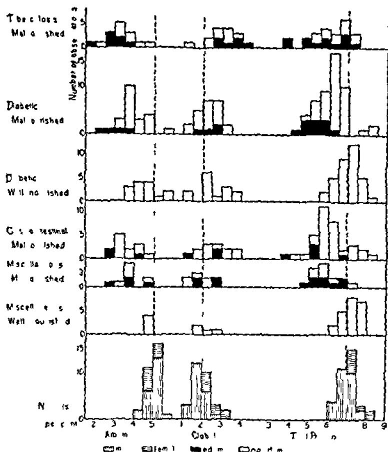


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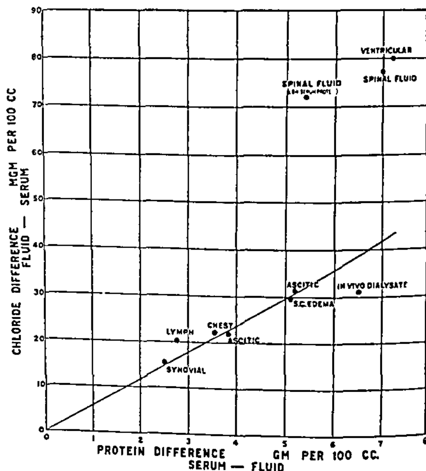


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authorities even advanced this effect as evidence of an abnormal hormone in hyperthyroidism Steyrer showed however that even in marked hyperthyroidism such tissue wastage could be reduced nearly to the normal level (1907) provided large amounts of carbohydrate and fat were supplied to cover the high caloric requirement characteristic of this disease state In fact Lauter and Jenke (925) were able by this means to achieve a normal minimum nitrogen excretion in hyperthyroid patients Similar results were obtained by Janney and Isaacson (1918) in hyperthyroidism artificially induced by injections of thyroxine Moreover Boothby Sandiford Sandiford and Slosse (1925) found 1 0 to 1 5 grams of protein per kilo daily adequate in marked hyperthyroidism provided the total calories in the day s diet totalled from 3000 to 5000 calories

When myxedematous patients are treated with thyroid preparations the apparent increase in protein catabolism is largely due to the elimination of the mucilaginous edema fluid Boothby and his collaborators showed that this deposit protein consists of a tissue fluid containing about 2 per cent of protein nitrogen In the course of this excretion the blood non protein nitrogen may rise temporarily

In glycosuria whether idiopathic due to phloridzin or when following pancreatectomy protein wastage has long been recognized as a classic symptom It occurs concomitantly with the wasting of tissue carbohydrate and has been elaborately described in terms of the D N ratio in the urinary excretion Von Norden s overproduction theory championed by the late J J R Macleod (1928) would consider the excessive protein catabolism merely as part of the general overproduction of the body s stores of energy The alternative explanation is a failure to spare protein because sugar though present is not metabolized A somewhat similar situation has been described in pituitary disorders Thannhauser and Curtius (1924) for example found a high nitrogen catabolism in a case of acromegaly The effects of these various endocrine disturbances as Houssay (1936) Long and Lukens (1935) and others have shown doubtless involve a disturbed balance between several opposing metabolic trends each attributable to a single endocrine

It has long been disputed how much protein diabetics require in their diets Petren (1927) as well as McClellan and Hannon (19 6) has shown that diabetic patients can be kept in nitrogen equilibrium on extremely low diets e g 0 46 gm of protein per kilo and 2000 calories per day Petren has claimed that the diabetic individual s ability to economize protein reduced hi minimal requirement to very low levels Lauter and Jenke (19 5) however consider these low nitrogen turnovers as evidence of malnutrition in such patients It is true that Wilder Boothby and Beeler (1922) showed that a high protein intake might aggravate diabetes mellitus and that decided clinical improvement might follow the reduction of dietary protein Peters and Van Slyke (1931 p 303)

nitrogen output produced by adding a small amount of protein to the insufficient diet as reported by Weech and Ling (1931) in Chinese

Mason (19 4) has studied the nitrogen balance of obese patients who were being treated with low caloric diets containing less than one gram of protein per kilo of actual body weight Although at first there resulted a negative nitrogen balance, it appeared that nitrogen equilibrium might be established ultimately with a subnormal turnover of protein Peters and Van Slyke (1931, p 285) believe such a condition should be avoided because it constitutes true malnutrition despite the accompanying obesity

When water as well as food is denied an animal, the blood non protein nitrogen rises higher than it would in simple starvation Prolonged thirst alone produces per se increases in both blood and urinary urea Even more striking effects were produced by Mackay and Mackay (1924) in the rapid dehydration caused by intravenous injections of concentrated sucrose solution This effect is due to an actual augmentation of nitrogen catabolism and is evidence of the so called 'toxic destruction of protein The net effect is unlike that of ordinary diuresis which removes non protein nitrogen from the blood and tissues for excretion in the urine If dehydration be prevented the blood non protein nitrogen tends to fall Conversely, Hachen (1923) observed in diabetes insipidus that, when pituitrin checks thirst and diuresis a rise in blood urea occurs Similarly, in the diuresis occurring with chronic nephritis and ed ma water may be excreted faster than nitrogenous catabolites In consequence as Atchley found (1918) non protein nitrogen accumulates temporarily in the blood This phenomenon must be distinguished from a true increase in nitrogen catabolism

In the edema which follows protein malnutrition characteristic changes may be found There may be a temporary dilution of the blood which disappears with diuresis The plasma proteins fall particularly the albumin moiety (see Fig 15) Weech and Ling (1931) found the plasma globulin exceedingly variable The attendant drop in plasma oncotic pressure probably is causally related to the edema as explained in a previous section Nevertheless, the edema is influenced by other factors, notably by the ingestion of sodium chloride and sodium bicarbonate

Protein Requirement in Various Disease States

Endocrine Disorders and Protein Metabolism

Outstanding among the hormones which in excess, unduly hasten protein breakdown is that of the thyroid (Muller 1892–3) For many years it was believed that thyroid hormone produced 'toxic protein breakdown, and some

fact Shaffer and Coleman (1909) produced positive nitrogen balances in the later weeks of typhoid with diets that contained over 60 calories per kilo and at least 14 gm of protein

The question naturally arises whether the fever, per se may not be the cause of this abnormal protein breakdown Graham and Poulton (1912–3) produced fever by means of a steam bath and found however that such artificial fever up to 103° to 104° F by rectum did not greatly alter nitrogen catabolism Moreover in infectious diseases nitrogen catabolism may remain high for some days after fever has disappeared and does not closely parallel the degree of fever when it is present It would appear that both fever and autolysis of tissues are independent results of the toxemia rather than quantitatively related Wastage of tissue protein may be ameliorated by supplying two grams of protein per kilo but the effectiveness of such therapy will depend upon the severity of the illness In addition it is essential to give 50 or more calories per kilo in the form of fat and carbohydrate to supply adequate fuel and thus spare protein consumption

In severe infections like lobar pneumonia a high blood non protein nitrogen may be found in the absence of renal impairment Thus McIntosh and Reimann (19 6) found urea and phenolsulfonephthalein excretion to be little affected even when the blood urea was elevated as much as 30 per cent above normal They concluded that the increased blood urea simply reflected a more rapid break down of protein in autolyzing tissues rather than a failure of renal function Peters (1926) believes that the administration of sufficient fluid to yield 2 or 3 liters of urine daily usually will prevent such azotemia by washing out the excess of catabolites In short the toxic destruction of protein produces azotemia usually only when combined with dehydration or oliguria due to a cardiac renal cause

Protein Requirement in Nephritis

In nephritis nitrogen metabolism may be greatly influenced by albuminuria as described in a later section This urinary protein chiefly albumin does not represent metabolized protein but rather protein which is mechanically lost from the body It nevertheless constitutes a drain upon the organism s protein stores which must be replaced by food protein Peters Bulger Lee and Murphy (1926) showed that in nephritic patients with severe albuminuria the dietary protein could safely be estimated on the basis of total urinary nitrogen i e by the sum of non protein nitrogenous catabolites plus the unburned protein excreted To estimate the true protein catabolism however it is necessary to determine the non protein nitrogen in the urine

It is self evident that in nephritis an elevation of blood non protein nitrogen

point out however, that it is "uncertain whether protein that is used for growth or restoration of tissue, and therefore is not metabolized, can influence carbohydrate metabolism They suggest that one gram of protein per kilo of body weight using for body weight not the actual weight but the most desirable weight for the given patient would appear to be a safe standard For children probably 1 5 to 2 0 gm per kilo of desired body weight" should be given the quota diminishing as age advances Such diets, however, must be adequately covered with insulin

Thus in diabetes increasing the diet without insulin merely tends to increase protein breakdown In severe hyperthyroidism, on the contrary, the nitrogen minimum can be suppressed to normal values, provided a sufficiently high caloric intake is provided In short no "toxic destruction of protein has been found in these endocrine disturbances when uncomplicated The nitrogen partition likewise has revealed no ground for this belief

Fever

Fever is accompanied by an increased breakdown of body protein Indeed Kocher (1917) showed that the nitrogen minimum amounted to 20 per cent of the total caloric turnover in high fever as against 2 to 5 per cent in normal individuals or in exercising subjects Shaffer and Coleman (1909) demonstrated that the high nitrogen metabolism of fever could be suppressed if the fever were not too high by administering a high carbohydrate diet In this connection it is interesting that Fr Muller and others have shown that in high fever the carbohydrate depots are emptied rapidly Lauter and Jenke (1925) found that in croupous pneumonia the nitrogen minimum was about three times the normal value, whereas hyperthyroid patients with a higher metabolism gave normal nitrogen minimums After the crisis in pneumonia, however, normal values could be found depending upon the progress of resolution To what extent cell toxins or immune bodies influence these phenomena is not yet clear

During fever occurring in the acute infectious diseases both total metabolism and protein catabolism are increased above normal Many observations in patients suggest that the rapid protein breakdown is not due simply to the increased caloric requirement but is in large measure attributable to an active destruction of tissues Indeed, the first of these factors can be largely abolished if sufficient fat and carbohydrate be given to provide generously for the increased caloric requirement of the patient The toxic" effect, however is dependent upon the severity of the toxemia and is not particularly influenced by diet In practice it is impossible to separate these factors in a given case One can merely assert that, if the toxemia as measured by fever, is not severe a diet high both in calories and in protein will establish nitrogen equilibrium In

fact Shaffer and Coleman (1909) produced positive nitrogen balances in the later weeks of typhoid with diets that contained over 60 calories per kilo and at least 14 gm of protein

The question naturally arises whether the fever per se may not be the cause of this abnormal protein breakdown Graham and Poulton (1912–3) produced fever by means of a steam bath and found however that such artificial fever up to 103° to 104° F by rectum did not greatly alter nitrogen catabolism Moreover in infectious diseases nitrogen catabolism may remain high for some days after fever has disappeared and does not closely parallel the degree of fever when it is present It would appear that both fever and autolysis of tissues are independent results of the toxemia rather than quantitatively related Wastage of tissue protein may be ameliorated by supplying two grams of protein per kilo but the effectiveness of such therapy will depend upon the severity of the illness In addition it is essential to give 50 or more calories per kilo in the form of fat and carbohydrate to supply adequate fuel and thus spare protein consumption

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cannot often be accepted as evidence of increased protein breakdown because the elevation may be due to a combination of other factors, viz poor renal efficiency oliguria, or hyposthenuria In "nephrosis", or non hemorrhagic degenerative Bright s disease, where proteinuria is characteristically most profuse, the blood non protein nitrogen ordinarily is low (Levy, 1923-4) and plasma protein is subnormal Moreover Peters and his associates showed that when nephrotic patients were able to take high caloric diets containing considerable amounts of protein, such patients stored large quantities of nitrogen over long periods without any rise of their blood non protein nitrogen This finding suggested that the tissue proteins of such patients had been depleted and in brief that these patients actually were malnourished

This malnutrition is not wholly due to loss through proteinuria Increase in actual nitrogen catabolism measured by the non protein nitrogen in the urine, may occur in association with one of the several phenomena characteristic of the disease Infection often initiates the disturbance, and there may be repeated exacerbations of infection These usually are accompanied by fever and often by anorexia and gastrointestinal disturbance In consequence body protein is perforce drawn upon to meet the increased caloric requirement If the attending physician unwisely limits the intake of protein or the total caloric intake, further inroads must be made upon the body stores

Peters, Bulger, Lee and Murphy (1926) found that in this disease the protein catabolism measured by urinary non protein nitrogen excretion could be reduced to as low levels as in normal subjects They even found positive nitrogen balances when the daily protein catabolism was as low as 0 5 grams of protein per kilo Rabinowitch and Childs (1923) and others have found that clinical improvement frequently was attended by storage of protein and an increase of true body weight Such results, however, demand a diet far in excess of the calculated requirements

It is logical in the uncomplicated case of chronic nephritis without azotemia not to restrict protein but rather to supply liberal amounts Protein must in fact be supplied for three distinct metabolic purposes (1) to cover the usual nitrogen catabolism (2) to replace protein lost in the urine and (3) to restore wasted tissue Protein used for the last two purposes does not influence blood non protein nitrogen even in the nephrotic type of glomerulo-nephritis In fact, patients with chronic nephrosis and the nephrotic type of glomerulo nephritis behave like patients with malnutrition in that they are economical of protein If however progressively larger amounts of dietary protein are supplied enthusiastically eventually increase in urinary nitrogen will show that all the extra protein is not being used for tissue restoration Increase of the protein intake beyond this point say Peters and Van Slyke (1931, p 306) probably is unwise because nitrogen catabolism will increase They doubt

whether Epstein's (1917) diets containing as much as 140 gm of protein daily are advisable They advocate starting with one gram per kilo of body weight and then increasing the daily protein consumption by stages of 20 gm or more If a rise in blood non protein nitrogen occurs it may be wise to reduce the protein intake somewhat

It is interesting that the urea produced when excessive amounts of protein are consumed by these patients exerts a diuretic effect In fact Maclean (19 4) advocated the use of urea itself as a diuretic in nephrotic edema This type of therapy properly controlled by repeated determination of the blood urea level is preferable to the indiscriminate administration of excessive amounts of protein

In other types of renal disease nitrogen retention with high blood non protein nitrogen is much more common To a certain extent increased nitrogen catab olism is partly responsible for this finding Thus acute nephritis often has its onset in a general infection This so increases protein breakdown that in some cases the blood non protein nitrogen rises despite a relatively high urinary nitrogen concentration and a negative nitrogen balance A similar situation was demonstrated by Mosenthal (1914) in experimental uranium poisoning of moderate degree He showed that rises in blood non protein nitrogen were likewise found with an increased urinary nitrogen excretion again an indication of toxic destruction of body protein

In the earlier stages of chronic hemorrhagic or glomerular nephritis Ritchey (1922) has pointed out the occurrence of irregular periods of fever This often is accompanied by an increased blood non protein nitrogen due to increased protein breakdown Peters and Van Slyke (1931, p 309) add that even in the absence of fever nitrogen excretion may at times become unaccountably large suggesting toxic destruction of protein In addition there may be considerable urinary protein which must not be considered as resulting from toxic wastage of tissue although it does of course influence the protein requirement and the protein balance

The variations of nitrogen metabolism in nephritis must be considered not only in advising the protein intake but also in evaluating the determination of blood non protein nitrogen This latter is the resultant of so many factors that a single value is of little prognostic help Therapy should not be directed solely toward the goal of lowering the blood urea Due recognition must be given to the fact that chronic nephritis is a prolonged wasting disease Blood urea probably is merely an indicator of the trend of a complicated biochemical flux as shown by Bollman and Mann (1027) They implanted the ureters of dogs in the intestines so that urinary nitrogen excretion was continuously ab sorbed from the gut In this way they obtained a sustained elevation of blood urea nitrogen over 300 mg per cent without the appearance of symptoms of

intoxication Therefore although it is desirable that in the long run urea nitrogen remain low it is important to be certain that the nutrition of the nephritic patient be maintained at as high a level as is possible

In the later stages of the disease intermittent partial starvation with nausea or vomiting may force the patient to burn his own protein because of a caloric intake inadequate for his activity, which sometimes is markedly increased by irritability The result is a pernicious destruction of protein in a patient who would better be burning fat or carbohydrate "Dietary treatment to be successful must maintain nitrogen equilibrium" (Peters and Van Slyke, 1931, p 31?) During the vomiting of severe uremia it is desirable to spare protein by the cautious intravenous administration of glucose

Although no known nitrogenous metabolite has been identified as the prime cause of clinical uremia frequently it has been suggested that purgation might be used to increase nitrogen elimination in azotemic patients This procedure is founded on the false assumption that the nitrogen excreted by bowel represents protein catabolites Actually Peters found that fecal nitrogen is not abnormal in nephritis even when the blood non protein nitrogen is elevated Furthermore, fecal elimination can be increased only by severe diarrhea, when unabsorbed food and increased intestinal secretion are swept through the irritated bowel Purgation, too, has the untoward effect that it diverts water from the kidney

Much discussion has been given the question as to whether high dietary protein may injure the kidney, especially if it be already damaged In rats Anderson (1926), Jackson and Riggs (1926) and likewise the Mackays and Addis (1927) failed to produce a nephritis even after one kidney had been removed (Anderson) They found merely hypertrophy of renal tissue Newburgh and Clarkson (1923), on the other hand produced in rabbits arteriosclerosis and chronic nephritis by giving diets unusually high in protein Maclean, Smith and Urquhart (1926) recently have repeated Newburgh s experiments and find that such diets caused nephritis in rabbits only if they lacked greens They obtained the same renal lesion with diets deficient in greens but containing only the usual protein content The problem is not yet settled, but at present the evidence that high protein diets cause or aggravate chronic nephritis is at best equivocal

Various Pathological Conditions and Protein Metabolism

In advanced liver cirrhosis in 'surgical' conditions involving the liver and in diseases of the gall bladder and bile ducts, there may be found an increase in nitrogen catabolism to explain an increased blood non protein nitrogen The picture is apt to be complicated, however, by dehydration or renal insufficiency In acute yellow atrophy (Rabinowitch 1929), severe phosphorous

poisoning (Bang 1915-6) and in hydrazine or chloroform hepatitis (Stander 1924) the total blood non protein nitrogen may rise due chiefly to accumulating amino-acids Blood urea may even fall as in experimental total hepatectomy (Bollman Mann and Magath 19 6) and may actually disappear as in Rabinowitch s (1929) case A similar condition was found by Wakeman and Morrell (1930) in monkeys ill with yellow fever In such conditions protein catabolism may appear to be excessive but because of its abnormal course this is difficult to evaluate

Wallersteiner (1914) has reviewed the older observation on nitrogen excretion in malignant disease Although nitrogen equilibrium is readily achieved Lauter and Jenke (1925) believe that the nitrogen minimum may be double the normal value In chronic myelogenous leukemia, the nitrogen minimum was within normal limits The urea and ammonia components of the urine were low the uric acid high After radiation the nitrogen minimum increased uric acid being disproportionately increased

In severe toxemias of pregnancy there may be obvious nitrogen retention as evidenced by elevation of the blood non protein nitrogen Bunker and Mundell (1924) believe that this occurs only with pre existing nephritis Stander, Duncan and Sisson (19 5) however considered the rise as due to toxemia per se The picture is complicated by the effects of vomiting starvation dehydration and convulsions which though secondary may influence protein catabolism in themselves In disease of the cardiorenal variety also, an elevation of the blood non protein nitrogen may suggest an increased nitrogen breakdown Except in the febrile diseases like bacterial endocarditi however where toxic autolysis of protein occurs these retentions of non protein nitrogen usually are due to failure of nitrogen elimination rather thar to increased protein breakdown

Drugs and Nitrogen Metabolism

Most of the apparent increases in protein catabolism reported in association with drugs and anesthetics may well represent toxic destruction of protein connected with trauma shock and untoward reactions Such responses were found by Krause (1926) after repeated injections of foreign serum and various drugs Glaubitz (1921) reported toxic protein breakdown after poisoning with carbon monoxide oxalic acid lysol bichloride of mercury and potassium bichromate

Likewise Grabfield, Alpes and Prentiss (1923) found that as little as 1 gm of potassium or sodium iodide daily increased the blood non protein nitrogen of adults and usually their urinary excretion apparently due to increased protein catabolism

Clinical Considerations of Protein Deficiency

For practical clinical purposes protein deficiency may be defined as a condition characterized by a lack of available protein in the plasma and a tendency to edema and serous effusions Among the general causes of such a condition are several broad groups an insufficient protein intake, inadequate absorption of protein abnormally great loss or increased destruction of body protein and insufficient regeneration of protein Although protein depletion occasionally may develop acutely usually it is the result of a chronic condition

Protein want during war or famine is recognized only too well In ordinary civil life a similar result may be found among those too poor or too ignorant to obtain adequate food protein Far more common, however, is the limitation of protein intake because of anorexia secondary to underlying local or constitutional disease This is especially true in diseases of the digestive tract and particularly so in mechanical disturbances which induce vomiting Of course non surgical conditions like diabetes which involve a general dietary restriction may also result in protein deficiency

Excessive loss of protein occurs in several types of chronic disease In chronic gastrointestinal hemorrhage as in peptic ulcer or hepatic cirrhosis, a sudden massive hemorrhage may fail of adequate recovery through regeneration of protein The severe proteinuria of nephrosis is an obvious hazard and to a lesser degree other albuminurias In the later stages of hepatic cirrhosis and of mediastino pericarditis the repeated tapping or draining of effusions may suffice to remove serious amounts of protein along with the fluid

It is possible of course that in these conditions concomitant failure of regeneration of protein may be a significant factor As pointed out earlier at present the origin of albumin and globulin is a purely speculative question It is suspected by many authorities however, that in chronic degenerative disease normal regeneration of body and plasma proteins are interfered with sufficiently to produce a state of definite protein deficiency This is thought to be especially true of conditions involving prolonged fever e g subacute bacterial endocarditis pulmonary tuberculosis and malignant lymphoma Such conditions frequently also involve the toxic destruction of protein discussed in an earlier section Usually it is difficult however to evaluate a given patient s condition in terms of abnormal destruction as compared with diminished regeneration of protein

Failure of absorption of protein occurs in many conditions involving the gastrointestinal tract Long continued diarrhea is the most evident feature common to these varied disturbances which include both primary disease of the alimentary canal and secondary derangement of its function Ulcerative colitis, tuberculous enteritis and even malignancy of the lower bowel are among

the primary diseases which produce diarrhea In sprue pernicious anemia and beri beri changes in the intestinal mucosa and increased intestinal rate may seriously hamper the absorption of foodstuffs In consequence a secondary protein deficiency is superimposed upon a primary specific deficiency state

The Clinical Symptomatology of Protein Deficiency —The symptoms and signs of protein deficiency fall conveniently into two main arbitrary groups Because the patient must draw upon his body s reserves, marked wasting of muscles occurs and with this goes loss of strength and related difficulties Likewise because of the diminution in plasma protein there is a tendency to edema and serous effusions

C M Jones (1936) has pointed out several interesting clinical features of this tendency for fluid to accumulate in the tissue space or in the serous cavities Usually the edema is subcutaneous and because it is noted only in the extremities it may be assumed fallaciously to be due to cardiac or renal failure The degree of such peripheral edema properly diagnosed is a fairly good index of the severity of protein want Nevertheless even in the absence of peripheral edema an accumulation of fluid in serous cavities may occur In nephrosis in hepatic cirrhosis and in mediastino-pericarditis this situation is encountered not infrequently Fluid may also accumulate in the viscera themselves notably in the lungs but also in the heart and in the bowel wall (Jones, Eaton and White 1934)

Many patients with a low plasma protein content will not develop edema until the fluid intake be increased Likewise if vomiting or diarrhea be marked edema usually is not striking and may even be observed to disappear with the onset of the symptoms Equally important is the intake of sodium chloride without which tissue fluid cannot be retained In addition secondary effects are attributable to the presence of sepsis to altered capillary permeability and to the functional capacity of heart kidneys and liver Frequently edema develops after a combination of contributing causes such as vomiting hemorrhage excessive clysis and circulatory failure Especially when malnutrition accompanies gastrointestinal disease the necessary surgical measures tend to aggravate the existing lack of protein and the post-operative administration of fluid and salt is very likely to induce edema in a patient whose plasma onкotic pressure is low Malfunction of a gastroenterostomy stoma may result for example from an edematous swelling of the bowel wall and a partial obstruction may develop at the site of operation In this way an unavoidable vicious circle may be established of which rapidly developing visceral edema is the final stage

The Clinical Treatment of Protein Deficiency —As in most instances of pathology encountered in the clinic the treatment varies with the factors causing the disturbance In the acute depletion of protein such as may occur

after massive hemorrhage, early replacement of protein by early and repeated transfusions is desirable. Many such cases will in fact, be able to take an adequate diet only late in convalescence. Meanwhile it is essential to avoid administering too generous amounts of fluid and sodium chloride.

When simple starvation is the cause, the providing of adequate amounts of dietary protein is the obvious remedy. In so doing it is important that the protein be derived from sources yielding a rich assortment of amino-acids. Animal and milk proteins usually are preferred as previously described, although certain vegetable proteins like that of the soy bean, have had their vogue. Dietary treatment alone however often will not suffice, if a serious mechanical condition of the bowel requiring surgical intervention is present. In such a case recourse must be had to repeated transfusions, to limitation of fluid and of salt and even to emergency feeding by jejunostomy. Failure to recognize the need of such measures may add greatly to the hazard of surgery and presents a much graver prognosis. In chronic disease of the intestinal tract not amenable to surgical treatment, much the same considerations apply. When, however, failure of protein absorption is due merely to mucosal changes secondary to a condition like beri beri, it is often sufficient to focus attention simply upon the primary disturbance.

In chronic disease such as nephritis or hepatic cirrhosis it is important to exert every effort to maintain protein equilibrium. In those cases in which it is impossible to get the plasma protein elevated to a satisfactory level transfusions may be desirable at times for the temporary elevation which they afford. In borderline cases limitation of salt and fluids must be resorted to, and edema may be controlled temporarily by use of diuretics. For this purpose Fulton (1936) has shown that certain mercurial diuretics administered intravenously or by rectal suppositories, are convenient and effective.

Derangements Involving Special Proteins

Urinary Proteins

Benign Proteinuria. — According to Maclean (19 4) about 5 per cent of war recruits and soldiers showed protein in the urine while at rest and twice as many after muscular exercise. The callow rapidly growing easily excitable adolescent is particularly likely to show this finding. The so-called "orthostatic" albuminuria once ascribed to lumbar lordosis with pressure on the renal vessels, may be merely the result of activity. Vasomotor instability (Wallis 1919–20) seems especially predisposing and Uyeda (1923) found that drugs which act on the sympathetic or vasomotor systems influence the excretion of protein. Fear, exercise and cold baths may precipitate proteinuria. Under

these circumstances as much as 3 grams a day may be recovered in the urine of an otherwise normal individual

The origin of urinary protein still is *debated* but it seems likely that it is composed chiefly of serum proteins which escape through an abnormally permeable glomerular tuft In addition disintegrating renal epithelium in nephritis may contribute small amounts of protein Indeed Bing (1936) has studied proteinuria from the standpoint of its filtration through the kidney He has found that the total protein and albumin excretion varies with the creatinine clearance of Rehberg This finding he has interpreted as indicating a uniform excretion mechanism for protein i e filtration through glomeruli with neither secretion nor reabsorption of protein in the tubules Bing found that when the proportion of albumin increased in the blood it likewise did so in the urine Variations in the actual protein content of the urine he ascribed to individual peculiarity in the permeability of glomerular membranes This permeability he thought was affected by the protein content of the diet

TABLE XVIII

THE AMOUNT AND NATURE OF THE URINARY PROTEINS IN DIFFERENT TYPES OF NEPHRITIS
After Hiller McIntosh and Van Slyke (1927 p 243)

Type of Nephritis	Number of Cases	Number of observations	Grams per twenty four hours			
			Total protein	Albumin	Globulin	A/G
Nephrosis	5	23	15 8	15 1	1 3	21 6 Maximum
Amyloid nephritis	1	17	4 5	4 2	0 3	7 6 Minimum
			14 0	8 4	5 6	1 5 Average
Nephrotic glomerular nephritis	9	40	16 8	15 1	2 0	8 9 Maximum
			1 8	1 4	0 4	3 5 Minimum
Vascular interstitial glomerulonephritis†	10	76	12 7	9 8	2 9	4 2 Maximum
			4 5	3 4	1 2	3 1 Minimum
Acute nephritis	4	21	15 3	12 8	2 5	10 0 Maximum
			3 5	2 0	0 6	4 8 Minimum

Chronic active hemorrhagic nephritis of Addis
†Terminal hemorrhagic nephritis of Addis

Hynd (1925) has found the specific rotation of urinary albumin when isolated to be identical with that of serum albumin Observations on sulphur content (Grabfield and Prescott 1936) indicate however that the sulphur nitrogen ratio in urinary albumin is about 1 20 i e only half that of serum albu

after massive hemorrhage, early replacement of protein by early and repeated transfusions is desirable Many such cases will in fact, be able to take an adequate diet only late in convalescence Meanwhile it is essential to avoid administering too generous amounts of fluid and sodium chloride

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same composition in various specimens of this albuminous substance The large proportions of amino-acids of the aromatic series found to be present indicate that these proteins belong to a definite group Furthermore Meyler (1936) has obtained from normal bone marrow a protein with properties quite similar to those of this group Bayne Jones and Wilson (19) demonstrated that highly purified crystalline material yielded immune and allergic reactions that were highly specific Moreover they demonstrated immunological differences between at least two groups of Bence Jones proteins Robinson (1927) obtained similar results

Chemically the Bence Jones proteins usually are classified as albumose or proteose Svedberg has found the molecular weight of one sample to be 34 000 Its peculiar solubilities however are not typical of albumose of albumin or of globulin Hopkins and Savory (1911) have described the reactions to changes in temperature and pointed out that acidity and electrolyte content of the solvent influence the result Urea solutions dissolve it and hence a high urea content of the urine may prevent the discovery of the protein Accordingly it is advisable before testing urine to dilute the urine and adjust its acidity In urine under favorable conditions the protein begins to coagulate between 40° and 60° C and is completely precipitated between 65° and 75° C As the temperature rises to near the boiling point the precipitate begins to dissolve and disappears on boiling On cooling reprecipitation and subsequent solution occur in the reverse order The presence of albumin may confuse the test until it is removed by heat coagulation and filtering while still hot In the cold (Magnus Levy 1900) the protein is precipitated by 25 per cent nitric acid or 12 5 per cent hydrochloric acid

Perlzweig Delrue and Geschickter (1928) have studied the high serum protein values found with Bence Jones proteinuria A large proportion of the serum protein was globulin the euglobulin fraction predominating Only a small amount of Bence Jones body was present It has been noted (Wintrobe and Buell 1933) that high concentrations of Bence Jones protein in the blood may be found when urinary protein excretion is low

Disturbances of Specific Prosthetic Groups —In a few favorable conditions it has been possible to study changes in special proteins in which alteration of the prosthetic group is the outstanding feature In the case of hemoglobin several alterations of the heme radicle are known In acetanilid or in nitrite poisoning the organically bound iron is oxidized to the ferric state and methemoglobinemia ensues The protein is no longer able to carry oxygen reversibly and serves no useful purpose unless it be to protect the tissues against accidental cyanide poisoning It is soon destroyed or excreted Similar changes occur in blackwater fever as described in Vol V Chapt XVII-B Occasionally sulphemoglobin is found the heme group now having formed a sulphur derivative

min This probably does not constitute a serious criticism of the above notion as to the source of the albumin because Schenck and collaborators have shown that the proteins of the blood serum vary with the general metabolism Inouye claims also that ingested foreign proteins may appear in the urine

The quantity of protein found in the urine of apparently normal people may vary from traces to 3 grams daily (Peters and Van Slyke, 1931, p 708) In certain types of Bright s disease 10 grams daily is common and 20 grams not uncommon As hyposthenuria and uremia approach, however proteinuria diminishes possibly (Addis, 1927–8) due to advanced sclerosis of the renal parenchyma In Table XVIII (from Hiller, McIntosh and Van Slyke 19 7) are summarized the findings in nephritis Less copious are the albuminurias of cardiac decomposition acute infections and toxemias of pregnancy

Globulin in the Urine — Ordinarily only small amounts of globulin can be found in the urine, even with brisk albuminuria Pure globulin is almost never found (Kollert and Starlinger, 1936) Fibrinogen may be present, usually associated with inflammation of the urinary tract but occasionally in Bright s disease In benign proteinuria the globulin usually is less than one tenth of the albumin although rarely larger proportions of globulin are found In the syndrome known as nephrosis albumin predominates Usually it is tenfold the globulin and almost invariably five fold in amount Csatáry (1891) found however that in amyloid nephrosis' larger quantities of globulin appear In this condition he attached diagnostic importance to a urinary albumin globulin ratio below unity if the total urinary protein exceeded 2 per cent

In the nephritides the albumin globulin ratio in the urine tends to fall with progression or exacerbation of the disease and to rise in remissions Csatary believed this finding to be an aid to immediate prognosis Hiller, McIntosh and Van Slyke followed 15 cases of advanced chronic hemorrhagic nephritis with urinary albumin globulin ratios consistently below 5 Of these, 13 died within 18 months (1927)

Bence Jones Protein — A group of closely related proteins bear the name of Bence-Jones, who in 1847 (1848) described this peculiar protein appearing in the urine of a patient suffering from multiple myelomata of the bones Rosenbloom (192) estimates that only 80 per cent of patients with multiple myeloma excrete this protein and points out that it may be found with other diseases of the marrow or blood forming organs Among these are chloroma, tuberculosis arthritis, spinal cord tumor leukemia and multiple metastatic carcinoma in bone It has been estimated that the daily excretion of Bence Jones body may exceed the total mass of tumor present in the patient The amounts excreted often are variable Daily excretions from 3 to 70 grams have been recorded The protein may be found intermittently

Elementary analysis by Hopkins and Savory (1911) showed essentially the

same composition in various specimens of this albuminous substance The large proportions of amino-acids of the aromatic series found to be present indicate that these proteins belong to a definite group Furthermore Meyler (1936) has obtained from normal bone marrow a protein with properties quite similar to those of this group Bayne Jones and Wilson (192) demonstrated that highly purified crystalline material yielded immune and allergic reactions that were highly specific Moreover they demonstrated immunological differences between at least two groups of Bence Jones proteins Robinson (1927) obtained similar results

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Disturbances of Specific Prosthetic Groups — In a few favorable conditions it has been possible to study changes in special proteins in which alteration of the prosthetic group is the outstanding feature In the case of hemoglobin several alterations of the heme radicle are known In acetanilid or in nitrite poisoning the organically bound iron is oxidized to the ferric state and methemoglobinemia ensues The protein is no longer able to carry oxygen reversibly and serves no useful purpose unless it be to protect the tissues against accidental cyanide poisoning It is soon destroyed or excreted Similar changes occur in blackwater fever as described in Vol V Chapt XVII–B Occasionally sulphemoglobin is found the heme group now having formed a sulphur derivative

Harrop has shown that sulphides produced in the apparently normal intestine may suffice to induce extensive blood changes, as discussed in Vol II, Chapt XXIV The presence of these pigment derivatives may be detected in blood and urine with the aid of a spectroscope or a spectrophotometer In those cases of acute carbon monoxide poison, which recover, usually there is no extensive loss of hemoglobin because carboxyhemoglobin dissociates reversibly In the chlorotic type of anemia hemoglobin is not formed because sufficient iron is lacking to build the heme group in quantity

Wald (1934) has shown that a similar state exists in vitamin lack Night blindness associated with vitamin A deficiency, is caused by a lack of active visual purple in the retina This visual purple is a protein to which is coupled a carotinoid nucleus derived from vitamin A There is a continuous loss in visual purple which must be replaced with fresh protein coupled to the carotinoid In night blindness visual purple is restored within a day after the feeding of vitamin A with relief of the amblyopia

A similar condition obtains in vitamin B lack In this instance Warburg has shown that the so-called yellow respiratory ferment" is lacking This enzyme is a conjugated protein, as previously discussed in which vitamin B_2 constitutes part of the prosthetic group which is a flavine derivative In B_2 deficiency an oxidative mechanism in tissues is impaired in consequence (Wagner Jauregg Rauen and Moller, 1934) The effect must not be confused with a somewhat similar property of Vitamin B_1 (Gavrilescu and Peters 1931)

Somewhat analogous to chlorotic anemia is the colloid goitre found in iodine poor districts In such goitres great quantities of thyroid protein are found but the material is poor in iodine and practically devoid of thyroxin (Oswald 1902) In consequence it has no beneficial effect when administered in human myxedema Animals and men, however, rapidly accumulate effective thyroglobulin in such goitrous glands when the iodine supply becomes adequate In fact the goitre frequently diminishes under such circumstances Kendall and Simonsen (1928) have shown that in districts poor in iodine there is a cyclic response of the composition of the thyroid protein found in the thyroids of the native fauna The total iodine diminishes during winter, and the thyroxine moiety may even disappear

In marked hyperthyroidism there occurs a relative paucity of iodine due to the extraordinary amounts of hormone which the gland is called upon to deliver Salter and Lerman (1937) have emphasized that a striking feature of iodine therapy in exophthalmic goitre is the rapid genesis of new thyroid protein Gutman Benedict Baxter and Palmer (1932) moreover, have shown that at first the newly deposited protein contains little thyroxine despite the accumulating iodine Subsequently however the thyroxine moiety assumes a constant composition in the accumulating iodo protein Even in normal man however,

hyroxine rarely contributes more than a third of the iodine found in human thyroglobulin Harington and Randall (1929) and Foster (1929) believe the major portion to exist as the amino-acid diiodotyrosine

Recent work by Landsteiner and Jacobs (1936) has brought the problem of drug idiosyncrasy into the field of conjugated proteins These investigators have presented evidence to show that simple chemical substances several of them found in industry, may themselves produce allergy The results are quite similar to those in which a diazotized sample of the animal s own protein (Landsteiner 1924) has been used as antigen It is supposed that there occurs a natural coupling or association of these simple chemical substances with body protein, and thereupon an immune response occurs to the antigen The phenomenon has been suggested likewise as a cause of skin sensitivity and asthma exhibited on exposure to dyed furs (Cerdon 1920) It may even explain the generalized dermatitis which sometimes follows exposure to poison ivy or primrose (Bloch 1929)

In the category of prosthetic groups too fall the specific carbohydrate moieties which have been isolated from immune bodies Heidelberger and Avery (1924) have demonstrated that the antibodies produced by various types of pneumococcus antigen contain carbohydrate groupings which are specific for those types The carbohydrate fractions even after liberation from the parent protein retain their ability to produce specific cutaneous reactions (Tillett and Francis 1929) Seibert (1926) has isolated a crystalline protein which behaves similarly toward tuberculosis It appears that the chemical basis of immunity will be found in large part to rest upon specific prosthetic groups attached to protein In this sense the original theories of Ehrlich have found striking justification

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Sept 1 1937

CHAPTER V-A

THE CHEMISTRY OF CARBOHYDRATES IN RELATION TO DISEASE

By WILLIAM T. SALTER

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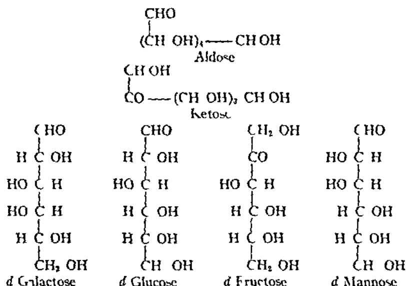
Physiological Basis of Carbohydrate Metabolism

PART IV

Nutrition and Carbohydrate

like ketones (e g fructose) Accordingly they were assigned the formulæ indicated in Diagram I

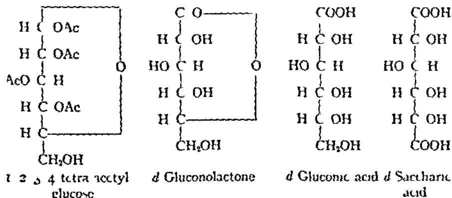
DIAGRAM I



It should be noted that dextrose is synonymous with glucose and levulose is synonymous with fructose

When acetate esters were formed with these hydroxyl groups however it was found that the hydroxyl of the fourth carbon atom failed to share in the esterification Thus the formula for 1 2 3 4 - tetra - acetyl *d* glucose was written as indicated in Diagram II

DIAGRAM II



1 2 3 4 tetra acetyl glucose   *d* Gluconolactone   *d* Gluconic acid   *d* Saccharic acid

PART I

THE CHEMICAL NATURE OF CARBOHYDRATES

The general term carbohydrates is used to signify those organic chemical substances which are composed of carbon C and water H_2O They correspond therefore to the general formula $C_xH_{2y}O_y$ and in metabolic processes can be considered sometimes as if they were a hydrated water soluble form of carbon For example it was known even before the time of Emil Fischer (1909) that blood sugar or dextrose had the composition $C_6H_{12}O_6$ and that when burned in the body the final outcome is simply that the six carbon atoms are oxidized to six molecules of carbon dioxide The rest of the sugar is of course eliminated as six molecules of water Such conceptions however will serve only the most primitive description of life processes Not all undoubted carbohydrates have the traditional composition as witness the methyl pentoses ($C_6H_{12}O_5$) and the digitoxoses ($C_6H_{12}O_4$) Furthermore there are carbohydrates or sugar derivatives which contain nitrogen like glucosamine ($C_6H_{13}O_5N$) Likewise some substances with the composition $C_xH_{2y}O_y$ are not carbohydrates at all e g methyloxyglutaric lactonic acid ($C_6H_8O_4$)

In general the carbohydrates in which the physician is interested are such substances as cane sugar dextrose or glucose milk sugar the cellulose of wood starch glycogen and agar agar The gums pectins and plant mucilages also consist largely of carbohydrate moieties

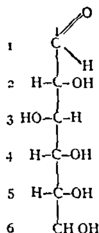
Composition and Structure of Simple Carbohydrates

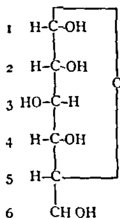
The general composition of the carbohydrates may be inferred from the empirical formula of the hexoses $C_6H_{12}O_6$ They contain approximately 40 per cent carbon 7 per cent hydrogen and 53 per cent oxygen Many of them crystallize with water of hydration which can be removed by drying or heating cautiously The differences between various carbohydrates are determined chiefly by the diverse combinations and permutations exhibited in their molecular architecture through sundry arrangements of their constituent atoms Although many carbohydrates contain one molecule of potential water for each carbon atom there are desoxy sugars in which one or more carbon atoms may have only hydrogen attached to them Thus rhamnose $CH_3(CHOH)_4CHO$ is a desoxy sugar or more specifically a 6 desoxy hexose

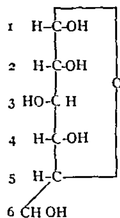
The hexoses contain five hydroxyl groups and therefore are polyatomic alcohols Originally they were divided into the aldoses and the ketoses because some behaved like aldehydes (e g glucose) and others

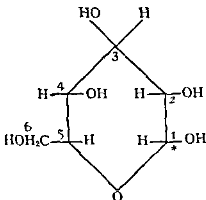
DIAGRAM IV

Different Methods of Representing α d Glucose with 1,5 Oxygen Bridge



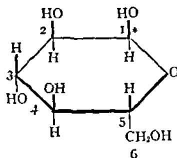






* = Reducing group

IV



* = Reducing group

V

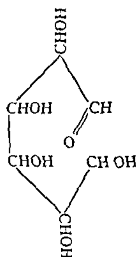
α-α forms of *d* glucose whereas cellobiose (from wood) is an α β combination (Diagram V) In both cases the diagram shows the α form of the disaccharide

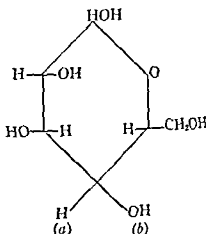
Various combinations of hexose are possible merely from the α and β forms as indicated in Diagram VI

This formula resembles that of the lactone of gluconic acid in that it contains a 1 5 oxygen bridge With oxidizing agents like bromine it is possible to convert glucose to the monocarboxylic gluconic acid More drastic oxidation e g with concentrated nitric acid, yields the dicarboxylic saccharic acid illustrated in Diagram II

When one studies the bonds between carbon atoms however and makes x ray studies of the crystal lattice in these hexoses it becomes clear that the molecule is actually curled about in zigzag fashion as shown in Diagram III

DIAGRAM III





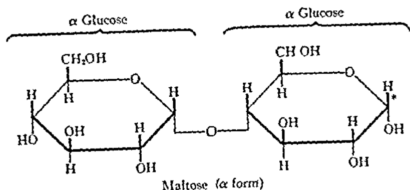
d Glucose

Consequently, one may write the formula of dextrose in several different ways according to the amount of information which one desires to connote in a given case (see Diagram IV) In formulæ IV and V the reducing group is indicated by an asterisk In these two formulæ the correct positions of the substituted H and CH_2OH groups on the fifth carbon atom are interchanged for typographical convenience

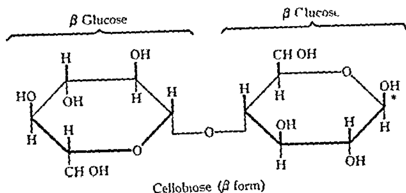
These six atom rings with the 1 5 oxygen bridge are referred to as pyranose forms It is possible also to have a 1 4 oxygen bridge which is referred to as a furanose or gamma configuration

Oligosaccharides — Just as the arrangement of atoms with reference to each other identifies the various monosaccharides so the oligosaccharides are recognized in part by the arrangement of hexose molecules with reference to each other Thus maltose (from starch) is made up of two

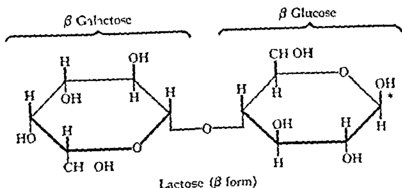
DIAGRAM VI



Maltose (α form)



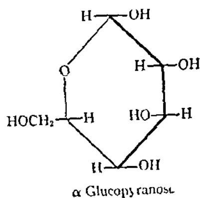
Cellobiose (β form)



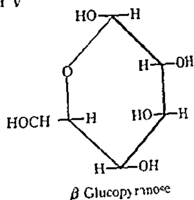
Lactose (β form)

After Haworth W N The Constitution of Sugars p 61 Edward Arnold and Company London 1929

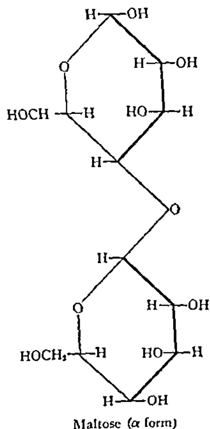
DIAGRAM V



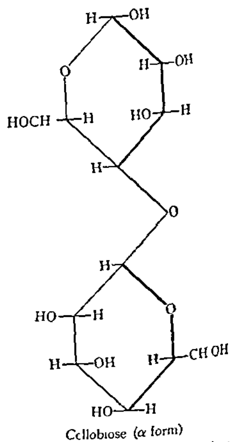
α Glucopyranose



β Glucopyranose



Maltose (α form)



Cellobiose (α form)

After Haworth W N The Constitution of Sugars p 60 Edward Arnold and Company London 1929

The same principles apply as the number of monosaccharide units in the molecule is increased Thus from cottonseed meal one obtains a trisaccharide containing galactose glucose and fructose in combination and named raffinose (Diagram VIII)

This raffinose can be hydrolyzed enzymically in two ways The enzyme emulsin splits off galactose leaving the sucrose combination The enzyme invertase however splits off fructose leaving a disaccharide of galactose glucose (combined) known as melibiose From gentian root another trisaccharide is obtained known as gentianose This is a combination of glucose glucose fructose When split with emulsin it

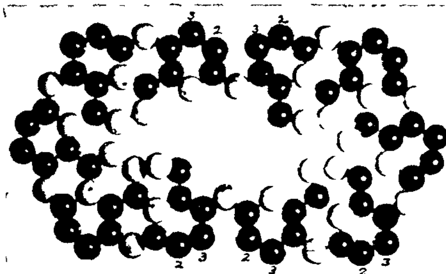


Fig 1 The constitution of starch This model constructed in three dimensions shows the five carbon atoms and single oxygen atom of each hexose ring The appended hydrogen and hydroxyl groups have been omitted After Haworth W N The Constitution of Sugars p 96 Edward Arnold and Company London 1929

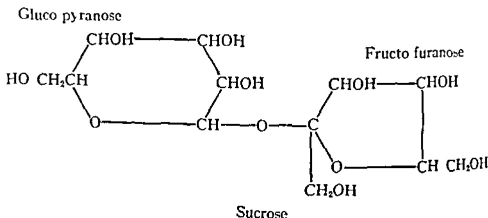
yields glucose and sucrose When split with invertase it yields gentiobiose and fructose It is evident that enzymes are useful agents in the laboratories of sugar chemists

Polysaccharides — In the glycogens or starches and the celluloses many units are combined It is convenient to think of the disaccharide maltose as the fundamental unit of starch or glycogen Similarly the disaccharide cellobiose constitutes the fundamental unit of cellulose (Diagram IX)

In Diagram VI the reducing group which affects alkaline copper reagents is shown by the asterisk

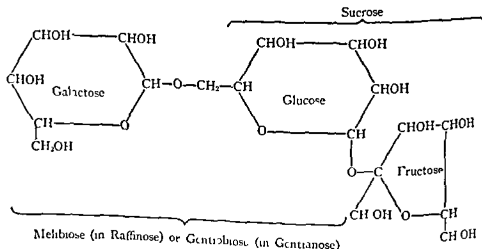
Further variety is provided by the fact that the two hexoses may be linked at various places in their respective molecules Thus sucrose (cane sugar) consists of a glucose fructose combination, joined through the two respective reducing groups (Diagram VII)

DIAGRAM VII



Sucrose

DIAGRAM VIII



In consequence sucrose fails to show any reduction with alkaline copper reagents although each of its separate components does so In other words sucrose is a reciprocal or mutual glucoside of dextrose and levulose

TABLE I

Substance	Unit	Link	Number of Units
Cotton Cellulose	Glucopyranose	β 1 4	200
Starch	Glucopyranose	α 1 4	26–30
Starch (Waxy Maize)	Glucopyranose	α 1 4	26–30
Glycogen (Rabbit Liver)	Glucopyranose	α 1 4	1 or 18
Glycogen (Fish Liver)	Glucopyranose	α 1 4	1
Glycogen (*Mytilus*)	Glucopyranose	α 1 4	18
Inulin	Fructofuranose	? 1 2	—
Levan	Fructofuranose	? 2 6	10–1

After Bell D J Recent Accomplishments in Carbohydrate Chemistry p 195 in Perspectives of Biochemistry Edited by J Needham and D E Green Univ Press Cambridge 1937

saccharide much as a railroad dispatcher thinks in terms of the individual car Thus a few monosaccharides two to six by convention may combine to form an oligosaccharide or many monosaccharide units more than six may join to form a polysaccharide molecule The classification arises in this fashion almost spontaneously *

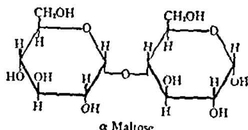
1 *Monosaccharides* i e simple sugars are distinguished further by the number of carbon atoms in the unit or molecule Thus pentoses contain five carbon atoms and hexoses six carbon atoms In most monosaccharides there is one molecule of water to each carbon atom but some monosaccharides contain less potential water There must be however at least one alcohol group and one aldehyde (or ketone) group on neighboring carbon atoms

2 *Oligosaccharides* i e disaccharides trisaccharides etc formed by the union of from two to six monosaccharide units

* In recent years other terms have been suggested Thus the Romance languages use the term glucide i e glucose like for carbohydrate Complex carbohydrates consisting entirely of carbohydrate moieties are called holosides whereas hybrid compounds of sugar with other substances are termed heterosides The non carbohydrate group in a heteroside is called either the aglucone or the genin Thus a heteroside consists of a holoside plus a genin

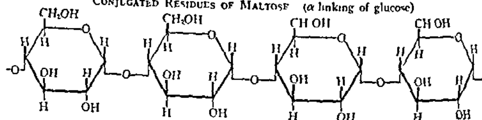
Actually such units are built up into mosaics as shown in Figure 1 As shown in Table I the number of glucose units so combined may vary from a dozen to two hundred Obviously the starch molecules

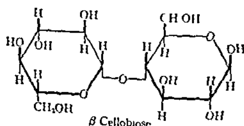
DIAGRAM IX



α Maltose

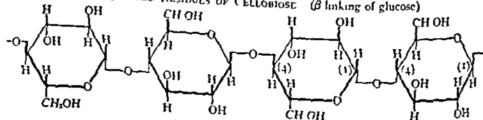
CONJUGATED RESIDUES OF MALTOSE (α linking of glucose)





β Cellobiose

CONJUGATED RESIDUES OF CELLOBIOSE (β linking of glucose)



approach the colloidal dimensions of protein molecules discussed in Volume I Chapter V

CLASSIFICATION OF CARBOHYDRATES

The classification of carbohydrates is among the most logical and clear of those known in biochemistry It adopts as its unit the mono-

The oligosaccharides of greatest physiological interest are the three disaccharides shown in Diagrams V VI and VII It will be noted that each of these contains a glucose unit combined with another monosaccharide Thus lactose is a glucose galactoside cane sugar is a glucose fructoside and maltose is a glucose glucoside These names are explained by Diagrams V VI and VII As will appear presently it is important for the chemist to know exactly how these units are conjoined and oriented because the constitution of saccharides is a matter of precise arrangement For example as shown above *d* glucose *d* glucoside is maltose which is well known as a food for infants and constitutes the simplest characteristic fragment of plant starch and animal glycogen In contrast to this is *d* glucose *l* glucoside or cellobiose which is useless as a food when ingested by man and constitutes the simplest characteristic fragment of cellulose or wood

Among the complex polysaccharides the polymers derived from the pentoses arabinose and xylose are known as pentosans These are complex substances analogous to cellulose and starch in the hexose kingdom They are the chief constituents of vegetable gums and mucilages Thus xylans are found in the hulls of oats in straw and in most types of wood Arabans are found in gum arabic and in cherry gum These pentose derivatives are not utilized by man but are important because herbivorous animals can obtain some energy from them Possibly this utilization is secondary to bacterial action in the gastrointestinal tract In man such materials are excreted unchanged in the urine

In the hexose series various complex anhydrides in addition to starch and cellulose are known For example many gums and substances like agar contain galactans i e a sort of starch composed of galactose Similarly fructosans anhydrides of fructose are found in the bulbs of onions and in the tubers of the Jerusalem artichoke From the latter inulin is obtained This on hydrolysis yields fructose which is an excellent food but unhydrolyzed it behaves as a foreign substance and therefore has been utilized in the study of renal function (Smith 1937)

The Constituents of Complex Carbohydrates

It has already been shown how by various modifications of molecular geometry new chemical compounds may arise The total number of such possible combinations obviously is enormous and it must suffice here to list a few of the commoner arrangements met with in physiological or nutritional processes

Oligosaccharides — The oligosaccharides of chief interest to physicians

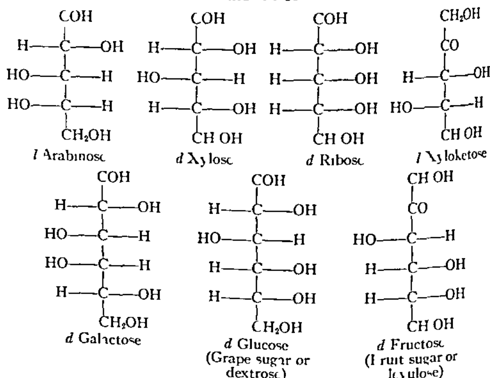
3 *Complex polysaccharides*, i e very large molecules formed by the union of more than six monosaccharide units

4 *Anhydrides and combined carbohydrates* This group we add to identify instances in which one loose end of a monosaccharide molecule joins with another part of itself to form a ring structure or unites with a non carbohydrate substance to form a hybrid molecule

Common Carbohydrates of Physiological Interest

Among the monosaccharides most commonly met with in the medical literature are the four pentoses and the three hexoses depicted in Diagram X

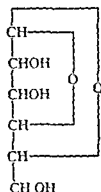
Diagram X

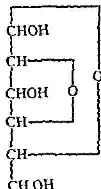


These are the ordinary building stones of which carbohydrates are formed and they play therefore much the same role as that described for amino-acids in the realm of protein structure as discussed in Volume I Chapter V Like the amino-acids they participate in the complicated metabolic transmutations which starches undergo in the animal body and serve either as fuel or to build body structure

they are excreted in the urine in copious amounts they do not react with the usual reagents used to detect urinary glucose Consequently the physician is likely to assume that the 'substitute has been utilized in place of glucose by body tissues

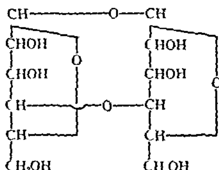
DIAGRAM XI





Hexosan <1 4> <1 5> 2,4 Anhydro hexose <1 5>

DIAGRAM XII



Hexose Derivatives — There occur also in the animal body chemical substances which represent slightly altered glucose molecules Among these are (1) glycuronic acid in which the sixth carbon atom has become acidic and (2) glucosamine in which an amino group replaces the hydroxyl group on the second carbon atom Many others are described by Tollens (1935)

are the following three disaccharides, each of which contains glucose

Maltose = glucose + glucose (less H_2O)
Milk sugar or lactose = glucose + galactose (less H_2O)
Cane sugar or sucrose = glucose + levulose (less H_2O)

Thus the four commonest 6 carbon monosaccharides hexoses occur chiefly in three combinations as disaccharides It should be noted that these substances are all glucosides because they are coupled through the oxygen attached to the first C atom in glucose As will appear later in the discussion of reducing power both maltose and lactose retain the reducing power of their respective second monosaccharide components because the linkage does not involve a group attached to the first C atom of this second unit In the case of sucrose however the reducing power of the disaccharide is obliterated because both components are coupled through groups attached to the respective number one C atoms Hence sucrose is referred to as a reciprocal glucoside of dextrose and fructose When sucrose is hydrolyzed or inverted as in digestion the coupling is split there results a mixture of equal parts of dextrose and levulose known as invert sugar

Trisaccharides also occur naturally and are of some importance as sources of carbohydrate for blood Typical examples are

1 Raffinose obtained from cottonseed meal which is a combination of galactose < glucose < > fructose as shown in Diagram VIII

2 Melezitose obtained from honey which is a combination of glucose < fructose < > glucose

Anhydrides — The anhydrides interest physicians chiefly because they have been suggested at various times as substitutes for ordinary sugars in the diet of sick people Otherwise they are of great importance only to organic chemists The anhydride is formed by the loss of a molecule of water from a sugar molecule with the resulting combination of two hydroxyl groups to form an oxygen linkage This may occur in a single hexose molecule Thus glucose glucopyranose 1 5 may form the anhydride glucosan (1 4) (1 5) The location of the oxygen bridges is shown in Diagram XI Similarly the anhydride linkage may occur between the two component monosaccharides in a disaccharide i e in such a manner that two couplings connect the component hexose molecules (Diagram XII)

In general the human body is not able to split such couplings In consequence these sugars are not utilized and are eliminated in the urine as foreign material More than one spurious ' cure for diabetes has been based upon the feeding of such useless carbohydrates Although

building stone whereas proteins comprise an assortment of different amino acids Thus from the pentoses arabinose and xylose are derived the respective pentosans of those sugars The formula $(C_5H_8O_4)_n$ indicates that a large number n of these monosaccharide molecules are coupled together to form a large molecule



$$NC_5H_{10}O \rightarrow (C_6H_8O_4) + NH O$$

Similarly cellulose starch and glycogen are formed from a combination of glucose molecules



$$NC_6H_{12}O_6 \rightarrow (C_6H_{10}O) + NH_2O$$

The number is estimated by Bell (1937) at from 12 to 200 according to the individual compound concerned as shown in Table I The dextrins which are analogous to peptones in the protein kingdom contain some two score hexose compounds per molecule The differences between these complex derivatives of glucose will be discussed in a subsequent section

Another complex polysaccharide is inulin which in recent years has been employed in tests of renal function (Smith 1937) This substance is a naturally occurring starch in which the building stones are probably exclusively *d* fructose molecules to the number of approximately 30 as found by Haworth and Learner (1928)

Physical Characteristics of Carbohydrates

When examined physically the sugars appear disappointingly alike The intriguing geometric complexities of molecular architecture just described produce no very obvious physical differences Most of the sugars and starches when pure are white solids which yield colorless solutions in water or alcoholic mixtures The starches yield colloidal solutions of high viscosity as do the pectins and plant mucilages Similarly the mucins in animals resemble viscous lubricants The more simple sugars can be differentiated crudely by taste Thus the sweetness of sugar can be arranged in descending order fructose cane sugar dextrose maltose galactose and lactose Absolute identification however requires analytical chemical procedures

A very useful physical property of carbohydrates is their ability to rotate the plane of polarized light Each sugar has its characteristic specific optical rotation which usually is read with the yellow D light of a sodium flame When viewed in a polarimeter this rotation may be used quantitatively to measure the concentration of pure sugar in solution or the rotation observed at a known concentration may be

Combined Carbohydrates — In recent years much information has been accumulated concerning the life history or fate of sugar molecules within the body Such studies have revealed that pentose and hexose molecules enter into combination with other chemical entities within the organism to form more complex molecules The isolation of these complexes by biochemists has yielded an assortment of chemical substances which are of interest chiefly in connection with the physiological role which each plays Some of these are described in the next section of this chapter

As described in Volume I Chapter V most proteins contain certain carbohydrate groups Ordinary serum albumin for instance probably contains mannose and glucosamine in combination (Rimington 1929) As noted also in Volume I Chapter V certain types of protein are so rich in carbohydrate components that they have been termed glucoproteid Among these are the mucins excreted by mucous membranes and synovial membranes the *chondromucoid* or matrix of cartilage and the *osseomucoid* of bone These last two substances were studied by Levene and La Forge (1915) who isolated from them chondroitin sulfuric acid the formula for which is given in Diagram XVIII on a later page

Chondroitin sulfuric acid on hydrolysis yields acetic acid glycuronic acid sulfuric acid and chondrosamine which is 2 amino galactose Obviously chondroitin sulfuric acid consists in (1) glycuronic acid combined (2) with a hexosamine i e a monosaccharide derivative containing nitrogen which has been acetylated and sulfonated Thus the carbohydrate basis of these mucoids may account for about one third of their mass

The nucleoproteins too and their derivatives contain pentoses among which *d* ribose is a common representative The nucleotides and nucleosides in which these pentoses occur will be referred to in a subsequent section in connection with the metabolism of muscle Thus, Levene and Jacobs (1910) found in the inosinic acid present in beef muscle a complex consisting of hypoxanthine *d* ribose and phosphoric acid Similarly adenylic acid has been identified as containing adenine combined with *d* ribose phosphoric ester In thymus nucleic acid *d* 2 ribodesose has been found

In connection with lipoid structure also it will be recalled that galactose occurs in the galactosides of brain tissue In short carbohydrate contributes to many structural elements in the organism

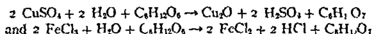
Complex Polysaccharides — From the simple saccharide molecules or their anhydrides and derivatives very complex molecules can be formed in much the same fashion that proteins are built from amino acids (see Volume I Chapter V) These substances often are colloidal in nature like proteins but are less varied in that they contain but one type of

dicated are polyatomic alcohols they can form esters with acids according to the general reaction

$R-OH + HO\ Ac \rightarrow R-O-Ac + H_2O$ where R represents the body of the carbohydrate molecule and AcOH is an acid like phosphoric or acetic acid In synthetic chemistry it is a common practice to block all of the existing free OH groups by exhaustive acetylation e g to form the penta acetate of glucose In Part II of this chapter will be described similar esters with phosphoric acid which have important physiological roles An analogous reaction known as methylation occurs with methyl alcohol with the elimination of a molecule of water Accordingly exhaustive methylation is used to block all of the free hydroxyl groups in common carbohydrates It should be noted that this process can be controlled so that for example if only the first carbon atom bears a methoxy group one has a simple glucoside methyl glucose either alpha or beta

Oxidation and Reduction — Dextrose may be oxidized by bromine water to form gluconic acid $CH_2OH(CHOH)_4\ CHO + O \rightarrow CH_2OH(CHOH)_4COOH$ This hexuronic acid has been described already in Diagram II Likewise dextrose may be reduced by activated hydrogen to form the hexatomic alcohol sorbitol $CH_2OH\ (CHOH)_4CHO + 2\ H \rightarrow CH_2OH(CHOH)_4CH_2OH$ Both types of reaction may result as the product of bacterial metabolism Such reactions of course serve to identify strains of related organisms

Of especial interest are the reactions of dextrose with alkaline copper reagents and with ferricyanide As mentioned later these reactions serve in colorimetric methods for measuring reducing substances like glucose The fundamental reactions involved may be written schematically as follows



$$2\ CuSO_4 + 2\ H_2O + C_6H_{12}O_6 \rightarrow Cu_2O + 2\ H_2SO_4 + C_6H_{12}O_7$$
$$\text{and } 2\ FeCl_3 + H_2O + C_6H_{12}O_6 \rightarrow 2\ FeCl_2 + 2\ HCl + C_6H_{12}O_7$$

Actually these reactions have been oversimplified in two respects First the actual color seen is produced by the addition of another appropriate reagent as described later Second these reductions of the reagent usually are performed in alkaline solution which in itself alters the carbohydrate

As shown by Nef (1913) in feebly alkaline solutions dextrose gives rise to other hexoses (see Diagram XIII)

Furthermore with stronger alkali a hydrolytic rupture of the carbon chain occurs In drastic treatment of this nature caramelization occurs numerous acids and aldehydes are formed and brown humus sub-

used in identifying an unknown sugar Specific rotation is defined as the angle α through which polarized light is rotated when viewed through two Nicol prisms between which is inserted a tube containing a 10 per cent solution of the sugar in question The equation expressing this relationship is as follows

$$(\alpha)_D = \frac{100\alpha}{l\ c}$$

The subscript D refers to the sodium flame $(\alpha)_D$ represents the specific rotation α the observed rotation l the length of the tube in decimeters and c the concentration of sugar per 100 c c of solution Thus Tanret (1895) showed that *d* glucose consisted of two isomers The β-glucose had a specific rotation of + 22 5° The α glucose gave the value + 110° Either of these substances when dissolved changed into an α β mixture of both forms with a value of + 52 5° This interconversion of the isomers is called mutarotation i e a change in rotation It reaches completion in several hours at room temperature but occurs much more rapidly in mildly alkaline solution In hot solutions the change occurs momentarily to form this equilibrium mixture which is characteristic and reproducible

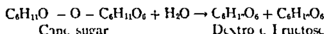
Viscosity is especially useful in measuring the concentrations of solutions of starch or gum The large molecules of these substances form gelatinous solutions and measurements of their rate of flow can be used to estimate concentration When a solution of starch or glycogen is acted upon by acid or by an enzyme the colloid is hydrolyzed into small sugar molecules At the same time the solution is found to flow more freely Indeed the progress of the splitting of starch can be followed conveniently by this means Similarly the concentrations of jams and jellies may be controlled in food laboratories by viscosimetry

General Chemical Properties of Carbohydrates

The important chemical properties of carbohydrates may be illustrated by the reactions of dextrose i e *d* glucose blood sugar or grape sugar Four types of reaction are especially useful in identifying and measuring the hexose in solution namely (1) oxidation and reduction reactions (2) the combination with phenylhydrazine to form a crystalline osazone (3) fermentation by yeast and tissue and (4) the formation of additional products containing amino groups

Esterification — Because the common carbohydrates as already in

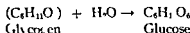
rupture however the connecting glucoside linkages between the components of oligo or polysaccharides Thus hot 0 5 normal hydrochloric acid will hydrolyze a 1 per cent solution of glycogen almost completely in an hour Similarly sucrose (cane sugar) is inverted to liberate its constituent dextrose and fructose components in the free state In this process a molecule of water is added



$$C_6H_{11}O_5 - O - C_6H_{11}O_5 + H_2O \rightarrow C_6H_{12}O_6 + C_6H_{12}O_6$$

Cane sugar Dextrose Fructose

Similarly the hydrolysis of glycogen adds about 11 per cent by weight of water to the animal starch

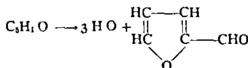


$$(C_6H_{10}O_5)_x + H_2O \rightarrow C_6H_{12}O_6$$

Glycogen Glucose

Recent work by Bell (1937) indicates that x in the above formula is 26 for many forms of vegetable starch as compared with 12 for animal glycogen (see Table I)

Heating with strong acids serves to distinguish between hexoses (6-carbon) and pentoses (5 carbon) For example dextrose yields formic acid $HCOOH$ plus levulinic acid $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$ Pentoses by contrast lose water and form furfural



$C_5H_{10}O_5 \longrightarrow 3\,H_2O +$ furfural (HC=CH, HC=C—CHO, ring closed through O)

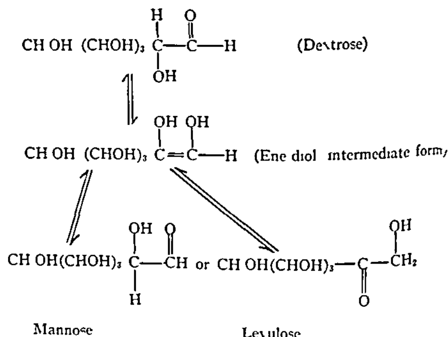
The furfural may be distilled off from such a digest and then detected by its forming bright colored compounds with aniline orcinol or other suitable substances In pentosuria described in a later section of this chapter this principle is applied in diagnosis

Reactions with Phenylhydrazine — Emil Fischer (1909) relied upon phenylhydrazine to a considerable extent in his separation and identification of various sugars With this reagent he was able to convert nondescript syrups into crystalline compounds with characteristic morphological appearance and distinctive melting points All monosaccharides and all disaccharides with a free aldehyde or ketone group combine with phenylhydrazine $C_6H_5 \cdot NH \cdot NH_2$ to form such compounds Thus dextrose yields an insoluble yellow crystalline compound known as phenylglucosazone which can be separated from solution and identified The reaction actually occurs in three stages as Fischer showed but the final product is $CH_2OH \cdot (CHOH)_3 \cdot C(=N \cdot NH \cdot C_6H_5) \cdot CH(=N \cdot NH \cdot C_6H_5)$ On

stances are produced In milder stages dihydroxyacetone CH_2OH CO CH_2OH glyceric aldehyde CH_2OH CHOH CHO and methylglyoxal CH_3CO CHO are formed These substances in turn may yield also glycolaldehyde CH_2OH CHO Because many of these fragments of the hexose molecule have a high reducing power the actual extent of the reduction of the reagent depends upon several factors which must be controlled empirically

In passing it should be noted that the fragmentation of dextrose in

DIAGRAM XIII

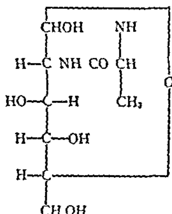


alkaline solution resembles in many respects the natural breakdown of sugar in body tissues This process is discussed further in connection with the intermediary metabolism of carbohydrates Unlike monosaccharides polysaccharides are resistant to the action of alkali An important feature of this resistance to alkali is its application to the chemical isolation of glycogen Thus Pfluger (1911) heated tissues like liver in from 20 to 40 per cent sodium hydroxide which split up proteins fats and other molecules but left glycogen intact The glycogen then was precipitated by adding alcohol in which it is insoluble

In contrast to alkali the action of acid upon hexose is less drastic and the carbon chain is not ruptured by mild treatment Acid does

sation products of glucose with amines have been made synthetically The simplest type of these involves merely the elimination of a molecule of water and the combination of the first carbon atom with the radical —N—HR In many instances this glucosidic form originates when *d* glucose is simply heated with the corresponding amine in alcoholic solution In other cases it is necessary first to form an acetobromglucose and then to allow the amine to react with the substituted bromine atom eliminating hydrobromic acid Presumably in nature this process is presided over by an enzyme system In the case of natural *d* glucosamine the amino group is substituted on the second carbon atom The

DIAGRAM XIV



synthesis was conducted originally by Fisher and Leuchs (1903)

The second problem is the combination of such amino sugars with other compounds because this combination is the basis of the structure of glycoproteins discussed in Part II Such combinations are not unlike the peptide linkage in protein described in Volume I Chapter V For example Bertho and Maier (1932) synthesized alanyl N-*d* glucosamine which as shown in Diagram XIV is chemically analogous to the peptides of aniline known in protein chemistry This mechanism serves to explain how amino sugars can be incorporated into larger molecules of biological importance

QUANTITATIVE DETERMINATION OF CARBOHYDRATE

The clinical laboratory usually is concerned with the estimation of glucose in body fluids In metabolic studies or in special investigations

treatment with acid the ketone aldehyde known as glucosone is formed $CH_2OH(CHOH)_3CO\,CHO$. This substance which may be reduced to fructose formerly was supposed by Hynd (1927) to be formed in the body by the action of insulin

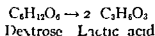
The osazones of different sugars can be identified because they have different melting points characteristic crystalline forms and somewhat different solubilities. Thus phenylglucosazone melts at 205° C galactosazone (from galactose) at 194° C maltosazone (from maltose) at 206° C and lactosazone (from lactose) at 200° C. Before inversion cane sugar (sucrose) forms no osazone because the disaccharide has no free aldehyde or ketone group. After inversion however the liberated glucose and fructose moieties each form the identical phenylglucosazone

Fermentation and Glycolysis — Fermentation of sugars is of two sorts in general i e alcoholic and glycolytic. The first type is performed by certain yeasts and by some bacteria. The mechanism of the process is discussed later as part of the metabolism of carbohydrate, but the gross reaction may be described as follows



$$C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$$

Glycolysis consists in the production of lactic acid from dextrose. Again the process is complicated as will be seen later. The gross reaction, however is a simple fission of the hexose molecule



$$C_6H_{12}O_6 \rightarrow 2\ C_3H_6O_3$$

Dextrose   Lactic acid

This process occurs in yeasts in bacteria especially acidophilus strains and in mammalian tissues. Embryonic tissues and exercising muscle produce large quantities of lactic acid when oxygen is lacking. Tumor tissue does so even when plenty of oxygen is available. This reaction of course is the basis for the primitive metabolism of fungi as Szent Gyorgyi (1937) has emphasized and represents a stage in chemical evolutionary development which preceded the ability to consume oxygen rapidly

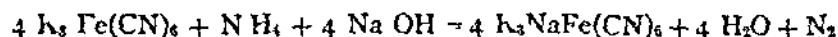
The Reaction of Sugars with Amines — It will be evident from the description in Part II of the physiological role of amino sugars and their derivatives that the body cells are able to incorporate amino groups into carbohydrate molecules with ease. As regards biochemical processes two types of combination must be distinguished first the incorporation of amino groups into the sugar molecule and second the reaction of such a molecule with other materials to form a more complicated compound

There is little difficulty with the first problem because many conden

The ability to reduce these reagents depends upon the presence of the aldehyde or ketone group in the sugar molecule but different sugars show various degrees of reduction Thus Hawkins (1929) found the following relative effect upon ferricyanide for different sugars glucose 100 mannose 101 galactose 79 fructose 98 arabinose 94 xylose 100 maltose 72 lactose 72 Bertrand (1906) has given somewhat different relative values for copper reagents When cane sugar is inverted as described in a previous section the mixture of glucose and fructose reacts nearly as if the original sugar had been glucose By combining this value with another property more precise information may be obtained Thus the reducing disaccharide lactose is differentiated from glucose because it is not fermented by yeast This fact is useful in studying the urine of pregnant women when diabetes mellitus is suspected

The extent of oxidation even with a single sugar like glucose depends upon time temperature alkalinity and other conditions Ordinarily one molecule of glucose reduces six or seven molecules of ferricyanide and ten of cupric salt Obviously the other hydroxyl groups of the sugar molecule *may contribute to the effect*

Among the numerous methods available for measuring the cuprous oxide or ferrocyanide produced are gravimetric titrimetric colorimetric and gasometric procedures Of these titration and colorimetry have found greatest usefulness The many chemical devices employed in these analytical procedures bear witness to the ingenuity of modern biochemists In Benedict s titration method (1911) for example the cuprous salt is precipitated as a white sulfocyanate which thus allows the blue cupric salt to remain visible In the method of Shaffer and Hartman (1921A) the cuprous salt is allowed to reduce free iodine which may then be titrated $2\,Cu^{+} + I_2 = 2\,Cu^{++} + 2\,I^{-}$ Van Slyke and Hawkins (1929) follow the reduction of ferricyanide gasometrically by measuring the nitrogen liberated according to the following reaction with hydrazine



$$4\,K_3Fe(CN)_6 + N_2H_4 + 4\,NaOH \rightarrow 4\,K_3NaFe(CN)_6 + 4\,H_2O + N_2$$

There are many other recognized procedures each of which has its own special application or appeal

Since the treatise of Bang (1913) on the blood sugar there have been evolved many colorimetric procedures for use with minute amounts of blood Most of these depend upon the reducing effect of glucose in hot alkaline solution As Somogyi (1927) has pointed out the glutathione and ergothioneine in blood together with creatinine and uric acid also reduce the reagent These substances affect various reagents in different degree Peters and Van Slyke (1932) state that the last procedures of

the measurement of complex saccharides like glycogen or mucin may be indicated Special methods may be required also to study rare disturbances like pentosuria Physical and chemical methods of sugar analysis have been reviewed in detail by Browne and Zerban (1941)

Estimation of Glucose

Most of the methods used clinically to estimate glucose make use of the following properties its ability to reduce in alkaline solution salts of heavy metals like copper or salts of nitro aromatic acids its dextrorotation in a polarimeter the production of carbon dioxide when fermented with yeast The latter two properties are not often used As Peters and Van Slyke (1932) have pointed out none of these properties is peculiar to glucose Ordinary sugar determinations therefore, tend to be too high By combining fermentation and reduction the error due to non fermentable reducing substance can be minimized By assuming that this spurious sugar value is constant at about 25 mg per cent however one can set arbitrarily maximal values for the normal reducing effect which are adequate for many clinical purposes

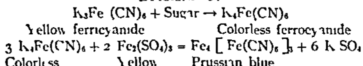
Another method of avoiding high non sugar reducing material is not to lake the red cells This device was employed by Folin (1930) in h use of unlaked blood filtrate Obviously the normal range of blood sugar varies with the method used Thus a blood sugar of 80 mgm per cent means hypoglycemia by the older Folin and Wu method whereas it is interpreted merely as a low fasting normal with the unlaked blood filtrate

The chief variations in the many modifications of methods for determining sugar by reduction consist in first the use of different oxidizing agents and second different methods of measuring the amount of this agent which has been reduced by the sugar

Since the time of Fehling (1849) various alkaline copper reagents have been used to detect sugar As described in a previous section the effect of glucose is to produce cuprous oxide Cu_2O as a red brown powder which in the older methods was weighed Later Bertrand (1906) introduced an accurate titration method which has been superseded by the method of Benedict (1911) for urine These methods however, are not readily applicable to the small amounts of glucose available in clinical samples of blood

Hagedorn and Jensen (1923) introduced the use of ferricyanide to estimate glucose The ferrocyanide so formed remains in solution is not readily reoxidized by air and can be determined easily by several micromethods

The ferricyanide procedure depends upon the Prussian blue formed with ferric salts as shown in Diagram XV



In order to screen out the two yellow colors contributed by the ferricyanide and the ferrous sulfate reagent an appropriate light filter is used

These various blood methods use different reagents to prepare protein free filtrate Among these tungstic acid and zinc salts are the commonest substances used as protein precipitants In the unlaked method of Folin sodium sulfate is added to make the solution hypertonic as described earlier

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Benedict (1931) and Folin probably yield results closest to true glucose values They show about 20 mgm per cent less "sugar than other methods In Table II are shown comparative results obtained in normal bloods by different methods In hyperglycemia the problem becomes even more complex because the non sugar reducer may increase and may affect different reagents in different proportions

TABLE II
COMPARISON OF BLOOD SUGAR VALUES BY DIFFERENT METHODS
DATA INCLUDE BOTH NORMAL AND GLYCEMIC BLOODS*

Method	Mgm of Sugar per 100 c c Blood Compared with That by Benedict s (1931) Method Taken a 100		
	Average	Maximum	Minimum
Shaffer Hartmann Somogyi copper titration	121	149	109
Folin ferricyanide colorimetric	98	124	86
Van Slyke Hawkins ferricyanide gasometric and timing method	120	138	115

* Data of Van Slyke and Hawkins (1929) summarized by Peters J P and Van Slyke D D Quantitative Clinical Chemistry Vol II Methods p 455 The Williams and Wilkins Company Baltimore 193_

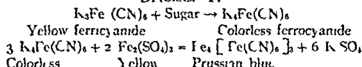
Of the many blood sugar methods now available for clinical use the following deserve special mention the ferricyanide titration of Hagedorn and Jensen (1923) the colorimetric ferricyanide method of Folin (1929) the colorimetric copper method of Benedict (1931) the copper titration of Shaffer and Hartmann (1921B) and of Somogyi (1926 1927) and the timing ferricyanide method of Van Slyke and Hawkins (1929) The first three can be used with as little as 0 1 c c of blood The last method is the simplest and the least time consuming

With the development of convenient instruments which apply the photo electric cell to colorimetry colorimetric methods doubtless will be used in clinical laboratories even more than previously One such instrument has been used successfully by Summerson (1939) for many types of analytical procedure Other instruments are being developed and improved each with its own advantage and appeal (Salter 1940)

In the colorimetric copper method use is made of a blue colored reduction product of phosphomolybdic acid The molybdate reacts with the Cu^{+} ion cuprous salt to form products of blue color the intensity of which measures the extent of reduction of the copper and by inference the amount of sugar present

The ferricyanide procedure depends upon the Prussian blue formed with ferric salts as shown in Diagram XV

DIAGRAM XV


$K_3Fe(CN)_6$ + Sugar → $K_4Fe(CN)_6$
Yellow ferricyanide — Colorless ferrocyanide
$3\ K_4Fe(CN)_6 + 2\ Fe_2(SO_4)_3 = Fe_4[Fe(CN)_6]_3 + 6\ K_2SO_4$
Colorless — Yellow — Prussian blue

In order to screen out the two yellow colors contributed by the ferricyanide and the ferrous sulfate reagent an appropriate light filter is used

These various blood methods use different reagents to prepare protein free filtrate Among these tungstic acid and zinc salts are the commonest substances used as protein precipitants In the unlaked method of Folin sodium sulfate is added to make the solution hypertonic as described earlier

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PART II

PHYSIOLOGICAL IMPORTANCE OF CARBOHYDRATES

Practicing physicians usually think of carbohydrates in terms of their caloric content with the tacit assumption that they are a convenient form of fuel From the standpoint of physiological behavior however these substances play many specialized roles in which the production of energy is not the immediate problem As will appear presently they comprise a large portion of the body s supporting structure Indeed the chitinous skeletons of animals like *Limulus polyphemus* the horseshoe crab and the framework of many insects are composed of cellulose like compounds of glucosamine In the human body similar compounds make up the gristle cartilage and other connecting tissues and contribute to mucilaginous lubricating fluids Carbohydrate radicals likewise contribute to the specificity of antibodies and enzymes

Glucose therefore is essential for the maintenance of structural equilibrium and also serves to sustain functional or chemical equilibrium among tissues Indeed its constant presence in the circulating blood and body fluids is essential to life as will be described later

Fuel for Emergency and Maintenance Requirements

The classical experiments of Claude Bernard (1855) on the liberation of glucose by the liver are recalled frequently in the clinic in connection with brain injury or piqûre These pioneer observations led eventually to the findings of Stewart and Rogoff (1924) and to the emergency theory of Cannon (1931 1932) It is now common knowledge that under circumstances leading to excitement fear or rage the blood glucose may rise sufficiently to cause glycosuria The immediate source of this extra sugar is the glycogen stored in hepatic cells from which it is released when the organism is subjected to intense stimulation of the sympathetic nervous system or to the action of adrenin Levine and others (1924) have shown that in a marathon race this source of sugar may become exhausted with the result that the runner collapses in a state of hypoglycemia

Less well recognized is the necessity for maintaining a constant supply of blood sugar to vital organs like the brain and heart This feature has been demonstrated especially well in instances in which the liver has been removed Under such circumstances Mann and Magath (1922) showed

that in dogs from which the liver had been removed there was a continuous drop in blood sugar until the animal became moribund and died in convulsions These investigators found that the intravenous injection of glucose mannose maltose and glycogen revived such animals when death appeared imminent Likewise Herring Irvine and Macleod (1924) studied the ability of glucose derivatives to alleviate the symptoms characteristic of insulin hypoglycemia Their findings were complicated by the possible transformation of such compounds into glucose by the liver but nevertheless they demonstrated the marked specificity of glucose per se as an antidote for insulin

How peculiarly essential glucose is for normal physiological processes was demonstrated by the results of Drury and Salter (1934) who observed the effect of glucose derivatives upon hepatectomized rabbits In these studies the liver was removed from the rabbits by a modification of the technique of Markowitz and Soskin (1927) which involved a preliminary operation to occlude partially the portal vein and vena cava As a result large collaterals to these veins develop and after several weeks the occluded vessels may be ligated completely without embarrassing the circulation of the animal After the portal vein and vena cava have been tied hepatectomy may be accomplished readily by cutting the attachments of the liver and removing it

After operation such liverless animals require the continuous administration of glucose in amounts approximating 125 mgm per kilogram per hour If glucose be withheld the blood sugar will fall as much as 20 or 25 mgm per cent each hour so that the animal becomes prostrated in about three hours lapses into coma and dies in about three and one half hours This phenomenon is illustrated in Figure 2 At death the blood glucose probably is less than 15 mgm per cent

Such animals may be used to determine the action in the animal body of carbohydrates other than glucose To this end Drury and Salter (1934) injected intravenously at regular intervals the particular carbohydrate to be tested and determined the effect upon the survival of the animals and upon the blood sugar The net result of these experiments with hexose derivatives was their failure to prolong the life of liverless animals Moreover despite the administration of glucose derivatives the blood sugar values approximated closely those of control animals provided that the substance being tested did not itself reduce the analytical reagent used

This inefficacy of the hexose and triose derivatives as substitutes for glucose was the more striking because many of the substances used had been proved physiologically useful under other circumstances Such evi

dence for example included the formation of glycogen, the prevention of insulin shock or the increased elimination of glucose in animals suffering from diabetes mellitus or from phlorhizin poisoning In brief removal of the liver had deprived the animals of their ability to convert various sugar derivatives into glucose Such results indicate that the liver is

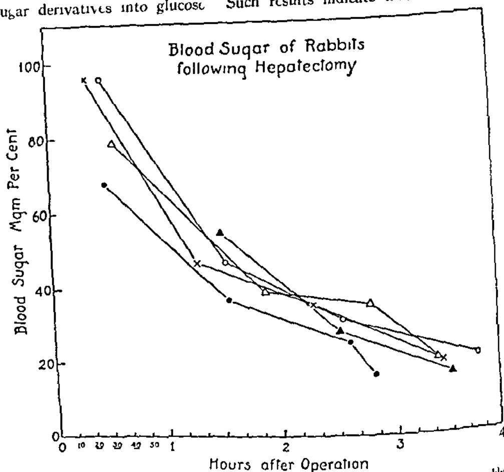


Fig 2 After removal of the liver from a rabbit the blood sugar drops steadily until death the time of which may be anticipated approximately After Drury D R and Salter W T Am Jour Physiol 1934 CVII 40,

readily capable of chemical syntheses of a complicated sort This finding will be discussed later

Obviously glucose was necessary for some essential tissue possibly the respiratory center Two possibilities existed namely (1) Brain tissue might require glucose for its metabolism just as most centers require oxygen, and when glucose is not available death results (2) On the other hand, glucose might be necessary for the environment of the

center just as calcium is necessary for the ... nervous tissues. The important lesson taught by ... servations was that the common indispensable ... was glucose, and that even slight modifications ... rendered it unacceptable as the source of the ...

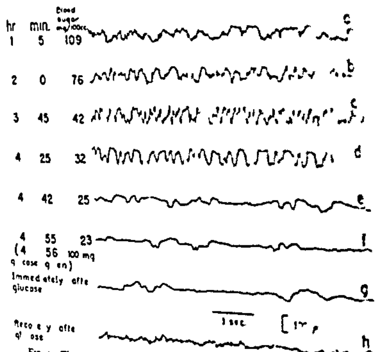


FIG. 3. The pattern of brain waves may be used to ... disturbance in brain cells during the hypoglycemia which follows hepatectomy ... Maddock, S., Hawkins, J. E., Jr. and Holmes, E. ... Am. J. ... Phys. ... CXXX ... 535.

Later Maddock, Hawkins and Holmes (1939) studied in greater detail the inadequacy of substances of the glucose cycle. This they did by measuring in the electroencephalogram the brain ... during the hypoglycemia following hepatectomy. Characteristic ... are shown in Figure 3. When such animals were given glucose, the ... cephalogram rapidly assumed a normal appearance as indicated in Figure 3. On the contrary, with the exception of mannose and maltose, no simple carbohydrate or its derivative was effective. The polysaccharides maltose and glycogen had a delayed effect, presumably because a ... time was required for their conversion by hydrolysis into glucose ... Maddock (1940) has found also that glycogen does not continue to ...

dence for example included the formation of glycogen, the prevention of insulin shock or the increased elimination of glucose in animals suffering from diabetes mellitus or from phlorhizin poisoning In brief removal of the liver had deprived the animals of their ability to convert various sugar derivatives into glucose Such results indicate that the liver is

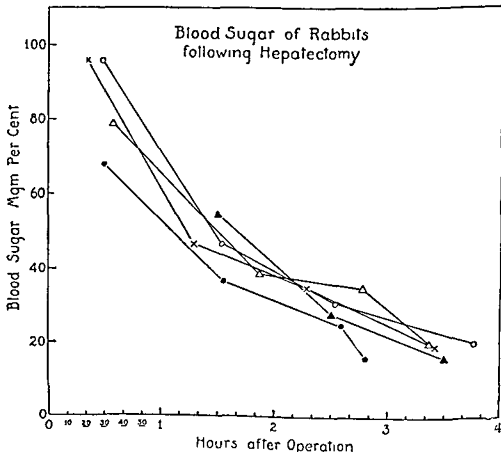


FIG 2 After removal of the liver from a rabbit the blood sugar drops steadily until death the time of which may be anticipated approximately After Drury D R and Salter W T Am Jour Physiol 1934 CVII 407

readily capable of chemical syntheses of a complicated sort This finding will be discussed later

Obviously glucose was necessary for some essential tissue possibly the respiratory center Two possibilities existed namely (1) Brain tissue might require glucose for its metabolism just as most centers require oxygen, and when glucose is not available death results (2) On the other hand glucose might be necessary for the environment of the

center just as calcium is necessary for the environment of cardiac and nervous tissues The important lesson taught by such experimental observations was that the common indispensable circulating carbohydrate was glucose and that even slight modifications in its chemical structure rendered it unacceptable as the coin of the realm

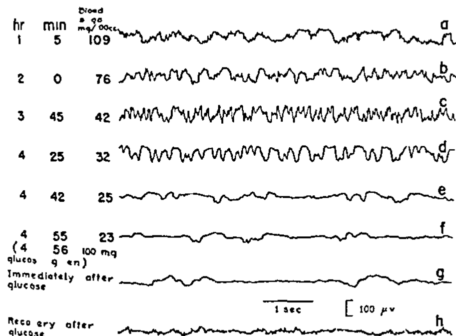


FIG 3 The pattern of brain waves may be used to identify carbohydrate disturbance in brain cells during the hypoglycemia which follows hepatectomy After Maddock S Hawkins J E Jr and Holmes E Am Jour Physiol 1939 CXXV 555

Later Maddock Hawkins and Holmes (1939) studied in greater detail the inadequacy of substances of the glucose cycle This they did by measuring in the electroencephalogram the brain potentials found during the hypoglycemia following hepatectomy Characteristic findings are shown in Figure 3 When such animals were given glucose the encephalogram rapidly assumed a normal appearance as indicated in Figure 3 On the contrary with the exception of mannose and maltose no simple carbohydrate or its derivative was effective The polysaccharides maltose and glycogen had a delayed effect presumably because a certain time was required for their conversion by hydrolysis into glucose itself Maddock (1940) has found also that glycogen does not continue to be

effective for as long a period as glucose In fact in the late stages after hepatectomy glucose no longer can be phosphorylated due to the disappearance of appropriate enzymes Blood from liverless dogs or rabbits at this stage may continue to split glycogen in vitro, but glucose fails to disappear as it would in normal blood

A great deal of similar evidence has been obtained by biochemical studies of the metabolism of isolated tissues It is impossible to review in detail this great mass of evidence but two series of experiments with tumor tissue may be cited as typical In the first of these Meyer McTiernan and Salter (1934) studied the utilization of simple derivatives of glucose by mouse sarcoma They used as a criterion of chemical change the production of acid by surviving slices of mouse sarcoma 180 in the presence of the carbohydrate under observation As will be described elsewhere the production of lactic acid by tumor tissue is a characteristic feature of the carbohydrate metabolism of tumors Meyer McTiernan and Salter (1934) found that glucose mannose and starch were available preeminently as sources of acid

Similarly Salter and Robb (1934) studied the effect of various carbohydrates upon the ammonia production by sarcoma In Volume I Chapter V it was pointed out that carbohydrate spares the protein breakdown in the whole animal The production of ammonia by cancer cells likewise may be diminished by carbohydrate material which the tissue is capable of splitting Salter and Robb found that as judged by this criterion glucose and mannose were nearly unique

In summary then with the possible exception of mannose the studies of isolated tissues and of reduced animals concur in demonstrating that glucose is unique as a common vehicle for transferring carbohydrate from one tissue to another and for transmitting it through the blood stream over long distances Furthermore without this substance the animal dies within a short time

Storage and Fixation of Small Carbohydrate Molecules

Most body cells in addition to the property of fixation of carbohydrate groups within special tissues such as connective tissue have also the property of forming large molecules of the type known generically as glycogen These molecules probably consist in a long chain of glucopyranose units joined to one another by a 1 4 oxygen linkage The number of these units varies with the source of the glycogen studied but in general it seems to be somewhere between 12 and 18 units for animal liver as described in Part I Although it was believed formerly that

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all glycogens were the same it is now clear that even in the same animal liver glycogen differs from the glycogen in muscles Thus Bell (1937) found that muscle glycogen of the horse consists in 12 glucose units as does horse liver glycogen and yet the muscle glycogen gives a blue color with iodine whereas the liver glycogen gives a reddish color This phenomenon has been studied in greater detail by Cori Cori and Schmidt (1939A) who believe that the finding is connected with the fact that the phosphorylase enzyme of muscle differs from that of other tissues In a certain sense therefore it could be said that the mammalian liver contains glycogen whereas mammalian skeletal muscles contain animal starch Many years ago Claude Bernard (1877) recorded finding the blue test with the glycogen of embryonic muscle but this observation lay dormant for several decades

It is intriguing that when fasting rabbits are fed galactose their livers contain a glycogen made up of 18 hexose units instead of the usual 12 This fact may explain in part why the liver glycogen of such animals appears more resistant to utilization than that of animals fed a normal diet

In recent years the work of Cori Colowick and Cori (1938) has modified previous ideas as to the chemical method by which this transformation of small molecules into molecular chains of colloidal magnitude is accomplished within the body Formerly it was thought that the transformation was effected entirely by the mediation of the enzyme amylase which is present in practically all tissues and which is capable of splitting both liver and muscle glycogens as well as vegetable starches After this enzyme has functioned in vitro one can isolate fragments of the original chain varying from a single unit of glucose to an average size of some ten units In fact Barbour (1929) using muscle extract was able to isolate a crystalline trisaccharide and Scharles and Salter (1934) obtained the same crystalline derivative by using extracts of sarcoma tissue It has been realized frequently however that the amounts of glycogen which can be broken down in a given time by the amylase present in body tissues are much smaller than many physiological circumstances demand Furthermore it was impossible to manufacture large amounts of glycogen from glucose through the use of tissue extracts containing amylase

These perplexities are now approaching resolution through the work of Cori Cori and Schmidt (1939B) whose observations concern the behavior of glucose 1 phosphate From this substance artificially synthesized considerable amounts of glycogen can be produced rapidly by tissue extracts under suitable conditions It is interesting that such a

mixture fails to produce glycogen until a tiny trace of glycogen itself be added. Thereafter glycogen is formed rapidly in large amounts. This reaction is reversible and because the amounts of phosphorylase or phosphatase enzymes in tissues are relatively large this reaction serves much more satisfactorily to explain how sugar can be mobilized rapidly or converted into glycogen as the occasion demands. There are other interesting sidelights on this process. For example it bears directly upon the explanation of phlorhizin poisoning because this substance affects phosphatase but not amylase. Furthermore Cori (1940) has shown that his ester is in equilibrium with other well known hexose phosphates known to be present in tissue extracts. This transformation is indicated by the following scheme

(a) The Cori ester (glucose 1 phosphate) is transformed under enzymic catalysis into (b) the Robison ester (glucose 6 phosphate) which is in equilibrium with (c) the Neuberg ester (fructose 6 phosphate) to form (b c) the equilibrium mixture of Embden (Embden s ester). This in turn may be converted into the Harden Young ester (fructose 1,6-diphosphate)

In this way glucose 1 phosphate may be viewed as the missing link between glycogen and the other phosphate esters which have been known for many years to be involved in the intermediary metabolism of carbo hydrate substances

Cori s ester also serves to explain another observation which concerns the energy cost of building up or breaking down large molecules. For example when glycogen is converted into glucose by amylase the process is one of simple hydrolysis with the addition of water and such a reaction involves relatively little energy. This would be fortunate from the stand point of bodily economy because sugar molecules could be transported thus from one tissue to another without great sacrifice of energy. It has been known for some time however that the formation of glycogen from glucose in the animal body requires the consumption of oxygen and the consequent sacrifice of relatively large caloric values. The reason for this is clarified by the finding of Kalckar (1939) that when glucose is phos phorylated oxygen must be consumed

As regards the fixation of glucose molecules however, in other spe cialized substances to be described later it may be said in general that this is a hydrolytic rather than an oxidative process. Accordingly it may be thought of as a far from wasteful method of storing sugar in the event that under stress such structural material need be consumed for energy. Such carbohydrate then could be regarded in much the same light as the dispensable protein stores discussed in Volume I, Chapter V

Role of Prosthetic Groups Antibodies Enzymes and the Antiscorbutic Vitamin

In the chapter on proteins (Volume I Chapter V) it was pointed out that the proteins are the bearers of special prosthetic groups which have to do with specific chemical reactions In particular we classify these reactions as being either (a) immunological or (b) enzymic but from a chemical standpoint there is little distinction between the respective mechanisms involved In recent years it has become increasingly evident that the character of the prosthetic group of antibodies and also of certain enzymes frequently can be explained on the basis of special carbohydrate prosthetic groups

Specific Carbohydrate Substances in Antibodies

Avery and Heidelberger (1923) undertook a study of the so called soluble specific substances which Dochez and Avery (1917) had discovered in fluid cultures of pneumococcus types I II and III As purification proceeded it became clear that the material was a polysaccharide When treated with hydrochloric acid the type II antibody solution lost its specific activity progressively as glucose was liberated Furthermore the respective soluble substances of types II and III were shown to be different because the latter could be thrown out of solution by an excess of hydrochloric acid Likewise whereas two thirds of the type II substance could be detected as reducing sugar mostly glucose after hydrolysis only 10 per cent of the type III substance assumed this form In fact some 85 per cent of the hydrolysis products of the latter consisted of a disaccharide acid $C_{11}H_{19}O_{10}$ COOH a so called aldobionic acid which *later slowly yielded glucose on hydrolysis* *In short* just as glycogen is a polysaccharide in which many units of the disaccharide maltose are linked together so this type III specific substance may be considered as a long chain molecule in which the repeated unit is the aldobionic acid Careful work along chemical lines has served further to establish the fact that the various specific soluble substances of the different bacterial antibodies have a distinctive composition For example it has been found (Enders and Wu 1934) that type I pneumococcus contains a labile acetyl group and furthermore that the material is an unusual nitrogen containing polygalacturonide On the contrary the specific polyaldobionic acid of type III pneumococcus is a constituent of the hemicelluloses and plant gums so that it is widespread in nature (Heidelberger 1936)

These various specific substances have distinctive physical properties which permit careful differentiation. Among the properties which are commonly used are the optical rotation of polarized light and the acidity both before and after hydrolysis (Heidelberger 1927). Thus the specific rotation for type I substance is about + 260° for type II about + 55 and for type III − 35°. Such values now have been obtained for thirty two different types of pneumococcus.

After hydrolysis into elementary monosaccharide units the various specific substances are found to be split up into their respective components for which special tests may be made. Thus type I yields an amino sugar whereas types II and III do not. Type III yields a levorotatory strong acid whereas type II yields a dextrorototary weak acid. Many of the differential properties particularly the effect of various precipitants have been tabulated by Brown (1939).

Although the various strains of pneumococcus have received the most extensive study similar specific soluble substances are now known for other bacteria. Thus Heidelberger Goebel and Avery (1925) were able to obtain a polysaccharide with specific properties from type B Friedlander bacillus. Many interesting experiments in the field of immunology have been made with such specific polysaccharides. It has been possible for example to couple such carbohydrates to the serum protein of an animal and by reinjecting this altered protein to produce antibodies to the bacterium in question. In fact under special conditions as for example on injection into the human skin such specific polysaccharides may even function as antigens and stimulate the production of antibodies. Landsteiner and Levene have hypothesized that this phenomenon may be due to the ability of these sugars to combine with certain tissue proteins and so to form new antigens (1925). Presumably the specific carbohydrate groups have an antithetical chemical relation to certain amino acid groupings in antigenic molecules much as a lock and key are related. In this wise might be explained the finding that when protein fractions of the tubercle bacillus the meningococcus and the streptococcus are injected into rabbits antibodies arise which react not only with the bacterial proteins but also with the specific polysaccharides of the organisms concerned. At present however although interesting quantitative studies have been made of this interaction there is no generally accepted explanation of the process. Much of the extant information on this subject has been surveyed by Heidelberger (1939).

Further work in the realm of organic chemistry remains to be done with these specific polysaccharides. First of all the detailed structure of each one must be worked out. Even in the case of type I pneumococcus

this information is not complete although it seems likely that the basic unit of the molecule is a trisaccharide containing an unidentified substance with two atoms of nitrogen plus two molecules of uronic acid of which at least one is galacturonic acid. Apparently the polysaccharide chains are not very long because recent studies of their molecular weight indicate a relatively small mass. The day doubtless will come when such prosthetic groups will be made synthetically and animals or men then will become immunized by this means to microorganisms with which they have never come in contact. In the case of viruses such immunization presumably also will be possible.

Plasma Proteins — Although we have been concerned thus far merely with bacterial proteins it is clear that the proteins of higher organisms also contain carbohydrate. Thus Rimington (1929) has studied purified protein of horse serum and found that part of it contains a carbohydrate derivative which is thought to be a disaccharide. This is made up apparently of the two monosaccharides mannose and glucosamine. It would appear therefore that specific soluble substances may be concerned with species differentiation such as is used in medicolegal tests. Incidentally Fränkel and Jellinek (1927) have reported the isolation from coagulated egg white and yolk proteins of a polysaccharide also containing mannose and glucosamine. Levene and Rothen (1929) believe this to be a trisaccharide composed of one molecule of glucosamine and two of mannose.

Enzymes

In the discussion of enzymes (Volume I Chapter V) it was pointed out that they owed their activity to specific prosthetic groups borne by proteins. In this respect the chemical action of enzymes and of antibodies presented striking analogies. In recent years the yellow enzyme of Warburg and Christian has been shown to bear vitamin B as its prosthetic group. In this complex the carbohydrate ribose serves as an intermediary link between the protein carrier and its flavine specific constituent. Further studies of the oxidative processes occurring in cells and involving compounds of another vitamin nicotinic acid indicate that there are two coenzymes which carry hydrogen from activated substrates to the flavoprotein. These coenzymes in turn contain carbohydrate as an essential link in their structure. Formulæ for cytoflave and coenzyme II appear in Diagram XVI.

Thus ribose a pentose is an important constituent of these vital substances. In this respect it plays much the same role as in the structure of the nucleotides found in the nucleic acids present in the nuclei

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and chromosomes of cells It has been known for many decades at least since the time of Kossel (1893) that an essential portion of nucleic acid structure was composed of the nucleotides Thus a purine or a pyrimidine base might be combined with ribose and phosphoric acid to form a nucleotide One of the most interesting of these is that composed of adenine ribose and phosphoric acid the so called adenylic acid which plays an important rôle in carbohydrate metabolism This substance may be hydrolyzed in two ways either (1) into phosphoric acid plus the nucleoside composed of adenine combined with ribose or (2) into adenine plus the phosphate ester of ribose As will appear shortly this carbohydrate containing material is extremely important in the chemical machinery of muscular activity

It is apparent then that carbohydrate serves many highly specific functions in biochemical phenomena which in the main are dependent upon specialized prosthetic groups

The Antiscorbutic Vitamin

The identification of vitamin C by Waugh and King (1931) as a hexuronic acid definitely established this essential substance as a six carbon compound with a relationship to glucose so close that a cheap commercial synthesis from glucose is possible Thus *d* glucose may be subjected to catalytic and electrolytic reduction to sorbitol which may then be transformed to *l* sorbose by selective fermentation This in turn yields an ordinary ketogulonic acid and eventually vitamin C is formed This series of chemical stages is illustrated in the formulæ in Diagram XVII The essential antiscorbutic effect depends upon the

Diagram XVII

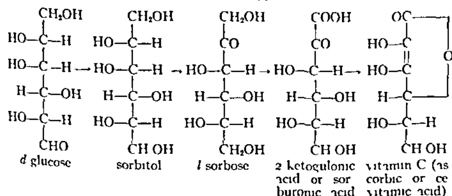
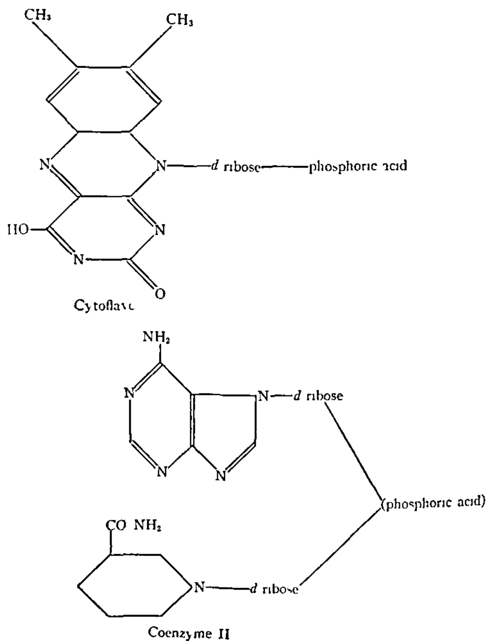


DIAGRAM XVI



Cytoflave

Coenzyme II

grow in the course of natural development The remnants of this earlier culture medium persist into and through adult life although we become aware of it only under exceptional circumstances For example Byrom (1934) points out that in myxedema the characteristic accumulation of myxoprotein or mucoprotein represents an overaccumulation of a material which is present in the normal individual Conversely in hyperthyroidism Boothby Sandiford and Slosse (1925) showed that there is an excessive loss of this mucilaginous matrix material Another example is scurvy in which as shown by Wolbach and Howe (1926) a solid or semi solid cement substance becomes liquid In like manner the cartilaginous supportive structures of the body the tendons the ligaments and even the collagen fibers of connective tissue exemplify this special class of matrix or connective substances

Chemically these substances all belong to the class of mucoproteins characterized by the fact that they consist in a long protein chain bearing a carbohydrate radical Their biological importance is twofold (1) the cementing or connective function as shown by their widespread occurrence in the linings of organs and (2) their lubricating and protecting function as evidenced by their presence in the secretions of hollow viscera and in joint fluids Bauer Ropes and Waine (1940) have reported for example that the synovial fluid of normal cattle contains a high concentration of mucin in the fore joints which bear heavy weight but a much lower concentration in the joints of the hind limbs

The chemical evolution of skeletal structures shows the following progression First in plants the chief supporting material is the nitrogen free polysaccharide cellulose Second in lower animals like *Limulus polyphemus* the horseshoe crab the chief supporting structure is a polysaccharide known as chitin consisting in long chains of acetylated chitosamine a sugar containing amino nitrogen Finally in the higher animals the long-chained element is taken over by protein but one still finds the carbohydrate prosthetic group This then is the stuff of which cartilage tendons aorta sclera and similar structures are made

In general according to Levene (1925) the mucoproteins may be classified as follows

1 Derivatives of mucoitin sulfuric acid A In this group are placed tentatively the typical mucins such as gastric mucin and salivary mucin Probably other materials less homologous also belong here such as the mucoid of ovarian cysts and the mucoid of serum and egg white

2 Derivatives of mucoitin sulfuric acid B In this group are the mucins of the umbilical cord of the vitreous humor and of the cornea When dilute acid is added to a saline solution of these materials a sticky

d configuration of the fourth carbon atom and the *l* configuration of the fifth carbon atom as demonstrated by Zilva (1935). It is interesting that whereas the natural compound is *l*-ascorbic acid and is the most active compound known, on the other hand *d*-ascorbic acid has no antiscorbutic effect. It should be added that the American Medical Association objected to the chemical name because of the implied therapeutic connotation and as the official term introduced the unscientific name, cevitamic acid; however, in 1940 New and Nonofficial Remedies the name ascorbic acid appears.

This material owes its acidic properties to the dissociation of an enolic hydrogen atom close to the double bond and not to opening of the lactone ring as would have been suspected with ordinary glycuronic acid. The compound is one of the strongest reducing agents known among naturally occurring organic substances. In alkaline solutions it is readily oxidized by air, but at reactions more acid than pH 7.6 it is autoxidizable only in the presence of copper or on exposure to light, especially in the presence of flavins. Of course it reduces methylene blue and indophenol dyes as well as hydrogen peroxide and free iodine. This reducing power presumably has an important function in connection with oxidation-reduction processes in nature because its oxidation product can be reversed readily by the fixed —SH (sulfhydryl) groups in proteins and in glutathione. The actual mechanism by which it functions in nature, however, is unknown. In aqueous solution it is dextrorotatory (24 degrees). Its first acid dissociation occurs at about pH 4.2. Careful studies of its reducing properties have been made by Ball (1937).

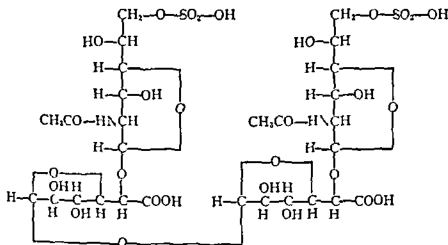
This material, although absent in dry seeds, appears within a few hours after they begin to germinate. Likewise the hen's egg is essentially free of vitamin C, whereas the newly hatched chick and indeed the embryo contain a great deal of it. Apparently all actively growing parts of higher plants, including green leaves, roots and buds, are rich in the vitamin. Most adult animals are able to synthesize the vitamin from glucose or closely related material. The important exceptions to this statement are (a) guinea pigs and (b) the primates, including man. The adrenal cortex is especially rich in this substance and seems to serve as a natural storehouse for the vitamin.

Tissue Matrix and Supporting Structures Lubrication Collagen

In the embryo, as is well recognized, there is a primitive matrix or intercellular cement substance into which primitive cells migrate and

The vitreous humor apparently contains a small amount of natural mucinase the activity of which possibly is connected with ascorbic acid This enzyme also degrades the mucin of synovial fluid or its polysaccharide This reaction can be observed to occur in two stages In the first stage there is a loss of viscosity and a change in precipitability with acetic acid In the second stage free amino sugars and reducing substances are formed by hydrolysis of the polysaccharide component Meyer Smyth and Dawson (1939) also have isolated from hemolytic streptococcus an enzyme which produces reducing sugars from the carbohydrate prosthetic *group of mucin It should be noted that the bacterial mucinase studied*

DIAGRAM XVIII



After Levene P A Hexosamines and Mucoproteins p 82 Longmans Green and Company London 1925

does not hydrolyze mucins from mucous membranes and glands but does split mucins formed by mesothelial tissues including that of synovial fluid It is suggested that this phenomenon may have some bearing upon the localization of rheumatoid arthritis

In recent years much work has been done upon the polysaccharide prosthetic group in mucin Meyer has isolated a substance of high molecular weight *from synovial fluid vitreous humor and umbilical cord* as well as from Group A hemolytic streptococcus This material which he calls hyaluronic acid consists of equimolecular parts of acetylated *d*-glucosamine and glucuronic acid

In harmony with the results with mucinase discussed above Meyer

flocculent mass precipitates which on stirring adheres to the rod much as fibrin does when blood is defibrinated by whipping

3 Derivatives of chondroitin sulfuric acid In this group are placed mucoproteins obtained from cartilage tendons aorta and sclera

4 Miscellaneous mucoproteins of uncertain composition Presumably the members of this group will be redistributed as they become better understood In this catch all are temporarily placed the mucoproteins of the skin of parenchymatous organs and of ovarian tumors containing either pseudomucin or paramucin Amyloid also may belong here

Carbohydrate Constituents of Mucoproteins

The precise arrangements of the atoms in the carbohydrate groups of the mucoproteins is a life work in organic chemistry which as yet is only partially explored In general the units of which the polysaccharide is constituted consist of (a) phosphoric acid (b) acetic acid and (c) a hexosamine in which an amino group is substituted on the second carbon atom of a monosaccharide unit In the case of the mucins this hexos amine is probably either 2 amino glucose or 2 amino mannose On the other hand in the case of the cartilaginous mucoproteins (Group 3) this material is thought to be 2 amino galactose known as chondrosamine (It may be remarked that chitosamine is 2 amino glucose epichitosamine is 2 amino mannose and chondrosamine is 2 amino galactose) A tenta tive formula for chondroitin sulfuric acid is given in Diagram XVIII picturing this substance as a substituted tetrasaccharide symmetrically constituted of two acetylated chondrosin sulfuric acid units It remains to be discovered through which grouping the material is linked to its native protein carrier but the free sulfuric acid dissociating hydrogen atom is suspect

Similar studies have been made with mucin from the umbilical cord the vitreous humor and the cornea From all of these sources Levene has isolated mucoitin sulfuric acid and identified its four components as consisting in equimolecular parts of acetic acid sulfuric acid glucuronic acid and hexosamine probably chitosamine

The mucins are not all identical in composition For example Robert son, Ropes and Bauer (1940) have studied the effect of mucinase an enzyme derived from an anaerobic bacillus *Clostridium perfringens* upon several types of mucin This enzyme did not attack gastric mucin sali vary mucin or chondroitin sulfuric acid derived from cartilage On the other hand mucins obtained from the umbilical cord from connective tissue fascia and from vitreous humor were all attacked rapidly by this enzyme

largely upon x ray diffraction studies Thus Clark (1934) studied natural cellulose fibers by x ray diffraction analysis and demonstrated their definite crystalline nature Later he showed that collagen fibers had a somewhat similar architecture and Clark and Schaad (1936) found a periodicity of 432 Å along the fiber axis which could be measured directly from diffraction interferences Because collagen is composed largely of amino-acids and is related in composition closely to gelatin it reasonably may be objected that it has no place in a discussion of carbohydrate substances The fact that partially purified collagen contains less than 1 per cent of carbohydrate distributed equally between glucose and galactose was ascertained by Grassman and Schleich (1935)

From a biological standpoint however Wolbach (1936) has pointed out that vitamin C appears necessary for the formation of intracellular substances which have collagen as their basis Moreover studies of guinea pigs suffering from vitamin C deficiency suggest that there is a quantitative relationship between the amounts of vitamin C administered and the amounts of intracellular substance produced Similar results were reported by Mazoué (1937) Such observations have raised the hypothesis that the carbohydrate in collagen is stationed at periodic intervals in the fiber to serve as coupling links connecting long chains of amino-acids As Bergmann and Niemann (1936) have pointed out it seems likely that the structural units of protein molecules in general are periodically arranged within the peptide chain Accordingly in the formation of collagen in vivo it is apparent that the natural growth processes must provide a mechanism capable of making a precise selection among the available structural units so that the complicated stoichiometrical pattern may be obtained Here indeed is an amazing example of a very complex specificity phenomenon

Is carbohydrate the natural connecting link between regularly recurring polypeptide chains in collagen fibers? Does this carbohydrate derive directly from vitamin C? If so the structure of collagen fibers as described by Astbury and Bell (1940) could be much more satisfactorily understood in terms of normal metabolic processes

Heparin

The discovery by Howell and Holt (1918–19) of the anticoagulant heparin has not only modified fundamental conceptions of blood coagulation but has contributed to modern clinical therapy Howell pointed out that this substance was formed of a complex containing uronic acids and sulfuric acid and recently the chemistry of this substance has been

Smyth and Palmer (1937) isolated two polysaccharides from pig gastric mucin The more abundant polysaccharide consisted in acetyl glucosamine and galactose in equimolar proportions the other contained acetyl glucosamine hexuronic acid and esterified sulfate, much as in hyaluronic acid

These polysaccharides are linked to proteins the nature of which seems to depend upon the individual sources Although it has been claimed that the combination is one of simple salt formation it remains to be proved that a firmer chemical linkage does not bind the protein and carbohydrate groups together This seems the more likely because the first stage of the breakdown of mucin is catalyzed by ascorbic acid peroxide and to a lesser extent by serum phosphatase

It seems likely that the viscous properties of mucins have a twofold origin Maximal viscosity is found when the carbohydrate prosthetic group is bound to its colloidal protein carrier Even the free carbohydrate material however has in solution a high viscosity, which disappears when it is split into its constituent components Thus in the original mucin the addition of a protein carrier merely exaggerates a viscous effect already present in the carbohydrate prosthetic group

Almost nothing is known about the formation and breakdown of these connective tissue and cement substances under physiological circumstances There is some suggestion that vitamin C belongs to an enzyme system which has to do with the formation of intercellular substance On this basis possibly some day the dental and arthritic signs in scurvy will be explained

In the field of physical chemistry systematic studies of the properties of these materials such as have been conducted in the field of protein chemistry during the past two decades, are only just under way Preliminary studies of viscosity and the variables influencing this property have been made by Bauer and Ropes Similarly collagen from tendon was studied by Astbury and Bell (1940) Its molecules were found to consist of long chained structures in which interatomic forces serve to contract the molecule into a more compact form after it has been stretched by an external force Thus the characteristic resiliency of a tendon is due in the last analysis to the natural elasticity of its constituent chemical molecules

Collagen

The evidence for this concept of collagen fibers as long chains of amino acids constituting a sort of crystal lattice which is elastic rests

It is suggestive that at a time when the infant's natural carbohydrate food consists largely of lactose i e glucose combined with galactose these galactose compounds are laid down as the nervous system continues to develop Nevertheless much of this lipid material has been formed already during fetal life so that one can not insist that there is a teleological connection between maternal lactation and the development of the infant's nervous system Moreover in Gaucher's disease as will appear in Part V deposits of kerasin are found in distended Gaucher cells in the spleen and other organs

The chemical behavior of these substances traditionally is considered in connection with lipoid metabolism or as part of the chemistry of the brain Accordingly they need not concern us further at this time

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In summary then it should be emphasized that carbohydrate must not be considered merely as a source of glucose the emergency fuel par excellence Important as this function is as the following sections will attest *it must still be remembered that important structural parts of* the body and indispensable enzyme systems together with the very nuclei of body cells themselves are made up in part of carbohydrate groups Moreover the specificity of immune reactions and the identity of certain species specific proteins depends upon the precise intramolecular arrangements which characterize the geometry of carbohydrate structure

March 1 1942

elucidated further by Jorpes and Bergstrom (1937) The material has been identified as mucoitin trisulfuric acid As pointed out by Jorpes (1939) it occurs in nearly all tissues especially in the lung It apparently is associated with mast cells and is set free in peptone shock or anaphylaxis It occurs in the walls of great veins and in this situation may be concerned especially with the prevention of clot formation

It is one of the strongest organic acids known Its close relation to chondroitin already described in a previous section suggested that other sulfonic acid derivatives of carbohydrate might have a similar effect This has been shown actually for derivatives of cellulose and of chitin Thus Chargaff Bancroft and Stanley Brown (1936) have shown a high inhibition of blood clotting by the sodium salt of cellulose disulfuric acid as well as the potassium salt of polyvinyl sulfuric acid The mechanism of action still remains under discussion but it seems clear that there is an antagonism between heparin and cephalin This fact suggests that heparin is connected with the action of antiprothrombin When heparin is appropriately neutralized with cephalin clotting ensues

The presumption is that heparin is present normally throughout the body to prevent coagulation of blood traversing normal tissue Therapeutically this property has been tried in a number of pathological conditions and at the present time (1941) offers considerable promise Such conditions are infections of the face with imminent or definite sinus thrombosis pyemia and massive pleural effusion It has been used prophylactically after surgical operations to prevent pulmonary embolus and is under trial in the treatment of subacute bacterial endocarditis

CEREBROSIDES

The hexose galactose contributes to two important constituents of the brain and other nervous tissue namely to the cerebrosides These are respectively phrenosin and kerasin Both of these lipids contain sphingosine combined with galactose and a fatty acid In phrenosin this acid is phrenosinic acid $C_{23}H_{67}OCOOH$ in kerasin the fatty acid is lignoceric acid $C_{23}H_{47}COOH$ Chibnall Piper and Williams (1936) have shown that these acids are not true chemical entities but rather mixtures of normal fatty acids Accordingly there must be several galactosides in the brain It is possible that in nature they occur combined with proteins in which case they would present an analogy to the mucoproteins in other tissues Unlike the other lipoids they are only sparingly soluble in acetone and by this property they can be differentiated They readily form stable suspensions with aqueous media

have shown recently by using radioactive carbon that even when sodium bicarbonate is administered to rats some of the carbon ends up in the liver glycogen

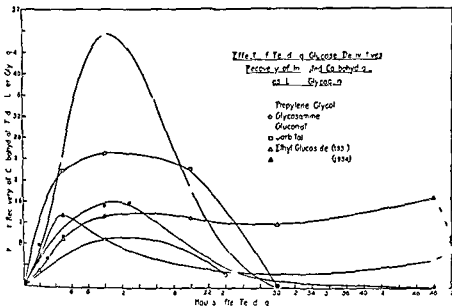


FIG 4 A heterogeneous assortment of rather different organic compounds can be transformed into glycogen by the mammalian liver After Salter W T Robb E D and Scharles F H Jour Nutrition 1935 IX o

Carbohydrate Containing Foods

In most naturally occurring foodstuffs the potential carbohydrate already is in hexose form or in some combination thereof Normally the bulk of carbohydrate food must be reduced to the monosaccharide stage before it reaches the blood stream from the intestine Although it is questionable whether any appreciable absorption occurs in the stomach it is clear that glucose can be absorbed high up in the small intestine and probably even in the duodenum (Trimble Carey and Maddock 1933) In general then for most natural foodstuffs the time required for the splitting of polysaccharide material is the limiting factor in the rate of assimilation

The polysaccharides as was suggested in Part II of this chapter are the natural form of storage for carbohydrate in plants as well as animals Some of these are useless for man especially the cellulose of

PART III

PHYSIOLOGICAL BASIS OF CARBOHYDRATE METABOLISM

ASSIMILATION OF CARBOHYDRATE

As suggested in Part II for many physiological purposes glucose appears to be the starting point from which metabolic processes involving carbohydrate proceed Thus although many types of compound which could not strictly be called carbohydrate ultimately may be transformed into carbohydrate within the animal body, such materials are not available as food for organs like the brain until they have been converted into glucose There is some suggestion indeed that they are first made into liver glycogen and then liberated as glucose or more strictly speaking that they are transformed into hexose phosphate The latter substance appears to be the common intermediate between glycogen and glucose which is capable of transformation either (a) into the polysaccharide form or (b) into the monosaccharide form according to the need of the organism The process of digestion and assimilation, therefore may be thought of as designed for the production of this common form of carbohydrate

The types of compound which may serve as carbohydrate food are extremely varied Thus it has been shown in Volume I Chapter V that amino acids like alanine may yield liver glycogen after deamination and therefore may be thought of as potential carbohydrates For this reason protein foods act as if they were approximately half antiketogenic Among the compounds containing only carbon hydrogen and oxygen which may serve to produce carbohydrate in the liver a representative number have been mentioned in Part II as being unfit for fuel in the absence of the liver Such simple substances as glycerin for example are excellent producers of sugar provided that those master chemists the hepatic cells are working efficiently Salter Robb and Scharles (1935) studied the rates of absorption of a number of these curious precursors of body glycogen both from the standpoint of the rate of absorption and of the effectiveness of glycogen formation Some of their results are pictured in Figure 4 Most of these substances were absorbed less rapidly than glucose and formed less liver glycogen The simple three carbon compound propylene glycol however proved itself an excellent source of liver glycogen It would appear that a great variety of chemical interactions are occurring constantly in the body particularly in the liver In fact Conant Hastings and their collaborators (1941)

have shown recently by using radioactive carbon that even when sodium bicarbonate is administered to rats some of the carbon ends up in the liver glycogen

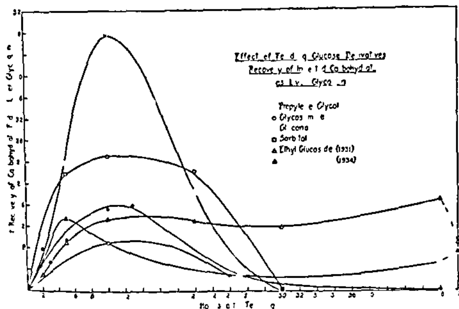


Fig 4 A heterogeneous assortment of rather different organic compounds can be transformed into glycogen by the mammalian liver After Salter W T Robb I D and Scharl F H Jour Nutrition 1935 IX 20

Carbohydrate Containing Foods

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The polysaccharides as was suggested in Part II of this chapter are the natural form of storage for carbohydrate in plants as well as animals Some of these are useless for man especially the cellulose of

fibers stems and the envelopes of leaves Likewise the cellulose capsules of grains protect the starch within from digestion, unless the capsule be broken

This capsule of course is the source of vegetable roughage or bran Ordinarily the fiber of cooked roots like turnips or carrots or the leaves of cabbage produce only a mild stimulation of intestinal peristalsis and pass out in the feces without causing cramps or diarrhea In the ptotic high strung individual however they may produce disagreeable effects Even the normal gastrointestinal tract rebels at too much coarse food of this sort although in times of famine or war it has been demonstrated repeatedly that a sort of tolerance can be built up gradually against excess roughage

Ruminants on the other hand are equipped to digest cellulose The four chambered stomachs of cattle and their capacious colons with enlarged vermiform appendix are obvious adaptations to an herbivorous life Sheep goats and horses have been described as walking silos and are capable of digesting as much as two thirds of a filter paper diet (Ellenberger 1916) Indeed Thomas and Pringsheim (1918) found that when filter paper was administered to a sheep 57 per cent of this nearly pure cellulose was digested Much of this splitting of cellulose is performed by intestinal bacteria which are essentially symbiotic Other organisms are equipped with enzymes which hydrolyze woods the ship worm (Harington 1921) and termite (Cleveland 1925) are notable examples In the latter case the specific action apparently is due to the presence of certain protozoa which play a symbiotic role

The chief polysaccharides assimilable by man are plant starches and animal glycogen which are derived from meat or liver To these should be added the disaccharides milk sugar cane sugar and maltose Maltose is utilized effectively when administered intravenously but cane sugar and milk sugar are essentially foreign bodies (Hogan 1914 Helmholz and Bollman 1940) unless they have been split by the intestine Ordinarily carbohydrate from ingested food reaches the blood stream in the form of one of four monosaccharides galactose glucose fructose or mannose

From the standpoint of assimilation the starches offer a distinct advantage over the sugars Solutions of sugar have a higher osmotic pressure and irritate the bowel Indeed 10 per cent glucose solution in quantities adequate for maintaining caloric requirements in man is not only nauseatingly sweet but is likely to produce diarrhea The starches however have little osmotic effect until they are split and absorption follows rapidly upon hydrolysis

Digestion

The object of digestion is of course to render carbohydrate sufficiently soluble to allow its passage through the intestinal mucosa into the blood stream so that it may reach the liver This absorption may occur either in the small intestine or to a less extent in the colon but probably little if any absorption occurs in the stomach The salivary ptyalin has a highly amylolytic action which persists in the stomach until the gastric acid renders it inactive but this salivary enzyme probably serves chiefly to remove starchy material which might insulate protein in the food from peptic digestion The greater part of the splitting of starches and dextrins occurs through the action of the pancreatic amylase which is poured into the duodenum through the pancreatic duct It is interesting that by toasting starchy food a partial breakdown of long starchy poly saccharide chains is effected This may convert them into dextrin like substances having as few as ten glucose units in the chain In this way digestion is greatly facilitated and goes on more rapidly a useful process for invalids The amylase then reduces these dextrin like substances to the disaccharide stage It probably acts only on alpha linkages as shown in Part I because it will not split cellulose which consists of beta linkages The disaccharides are then hydrolyzed by enzymes of the in testinal mucosa

The disaccharide fragments e g maltose or sucrose are split further into their two constituent monosaccharides Thus maltose from starch yields two glucose molecules and sucrose (cane sugar) yields one molecule of glucose plus one molecule of fructose Because it is a common tempta tion to inject cane sugar intravenously special note should be made of the following paradoxical fact When cane sugar is introduced artifi cially into the blood stream without first traversing the intestinal mucosa it is useless as food Even the versatile hepatic cells are unable to split it and therefore it acts merely as a powerful diuretic and dehydrating agent As the kidney acts to rid the system of this foreign body much water is excreted because of the high osmotic pressure of the dissolved sugar

Because glucose tolerance tests are dependent in part upon the rate of absorption of carbohydrate certain points affecting this process must be borne in mind Some of these have been studied in man and in animals by Abbott and associates (1940) by May and McCreary (1940) and by Groen (1938) For example it is not commonly realized that con centrated glucose solutions are irritating and may produce marked diar rhea When rats or mice are fed solutions of glucose as concentrated as 10 or 20 per cent within an hour their intestines will be found greatly

distended with syrup and the intestinal wall stretched to transparency Obviously the high osmotic pressure of the sugar within the lumen of the intestine draws out large quantities of body water In fact it has been claimed by some investigators that no great absorption of the dissolved sugar will occur until it constitutes a nearly isotonic solution If such animals do not die they relieve themselves by profuse diarrhea followed by a period of dehydration and anorexia punctuated by great thirst In human patients this problem is encountered often when rectal feeding of glucose is attempted concentrations above 5 per cent should be used with caution It is evident, therefore that when syrup is given by mouth its concentration of sugar may influence the rate at which glucose appears in the blood stream In diseases like sprue and celiac disease when the intestine is already abnormal delayed absorption may lead to a flat blood sugar curve which may be interpreted erroneously as evidence of defective handling of carbohydrate by the tissues proper

Absorption of Carbohydrates

As already pointed out the absorption of disaccharides and polysaccharides is conditioned by the splitting of these substances to monosaccharides The problem of carbohydrate absorption therefore resolves itself into the absorption of monosaccharides from the gastrointestinal tract into the blood stream Glucose itself is absorbed in both the small and large intestines Thus Bergmark (1915) found that more than three fourths of glucose administered by rectum in 15 per cent aqueous solution was absorbed in one hour

The rates of absorption of these simple sugars have been studied by Cori (1925) and others Such experiments have been conducted chiefly in rats and in rabbits and they involve a certain artificiality Indeed as already mentioned prostrating diarrhea may result from too generous feeding of these sugars in concentrations above 10 or 20 per cent With this limitation in mind however the rate of absorption in rats depends chiefly upon the sugar studied The rate is not influenced by the concentration of sugar used although the duration of absorption is determined thereby Galactose is absorbed most readily followed in order by glucose fructose and mannose The artificiality of such measurements is evident from the fact that galactose is absorbed most rapidly when fed alone less rapidly when mixed with glucose and still more slowly when chemically combined as milk sugar (Cori and Cori 1928A)

The net result of the digestion of carbohydrate then is much the same as if the monosaccharides had been injected slowly into the blood

stream The reducing power of the blood when measured with alkaline copper reagents increases owing to increased sugar concentration Despite the fact that the sugar newly absorbed from the gut must pass through the liver Cori (1925) was able to demonstrate unchanged galactose and xylose in the blood an hour after feeding Reinhold and Karr (1927) showed that galactose caused the greatest blood sugar rise glucose less and fructose least This result is in accord with the relative rates of absorption of these compounds The use of this postprandial hyper saccharemia in functional tests will be discussed later in connection with diabetes mellitus and liver disease In studying renal function use has been made of xylose because little or none of it is utilized by body tissues

From the blood the monosaccharides diffuse rapidly into tissue spaces Trimble and Carey (1931) for example found a rapid rise in the glucose of the skin following the absorption of glucose Likewise Cori and Cori (1928B) found that galactose definitely accumulated in the tissues before it exceeded the renal threshold Thus the fluids of the tissues particularly of the skin act as an overflow reservoir which buffers the post prandial surplus of free monosaccharide As the concentration of sugar in the blood falls the free sugar in the tissue fluids falls correspondingly (Stetson and Peters 1941)

Absorption of Hexoses in Man — Relatively few careful observations are available on the rate of absorption in man Groen (1937) however has used the technique of Miller and Abbott (1934A) to study the absorption of three hexoses glucose galactose and levulose The technique permitted a control of the length of intestine selected for study so that the corresponding rates of absorption per 50 cm length of bowel could be estimated Per 50 cm length glucose was absorbed at the rate of about 11 grams per hour galactose at 13 grams and levulose at 7 grams per hour The maximum absorption rate was influenced by the concentration of sugar solution administered For levulose the concentration was only 6 per cent as compared with 10 per cent for glucose In the course of absorption the glucose concentration in the duodenal contents was reduced to about 2 5 per cent i e to half of the isotonic concentration (5 4 per cent) The chloride in intestinal contents probably makes up the total osmotic pressure to that of blood plasma It should be noted that these results in man differ somewhat from the observations on rodents described earlier

The normal pyloric sphincter mechanism feeds glucose solution into the intestine gradually as pointed out by Holtz and Schreiber (1930) so that the intestine ordinarily receives no more sugar than it is able to

cope with Consequently 100 grams of glucose administered by mouth elevates the blood sugar curve no more than 15 grams placed by intubation directly into the duodenum Levulose causes distinctly less elevation than glucose or galactose

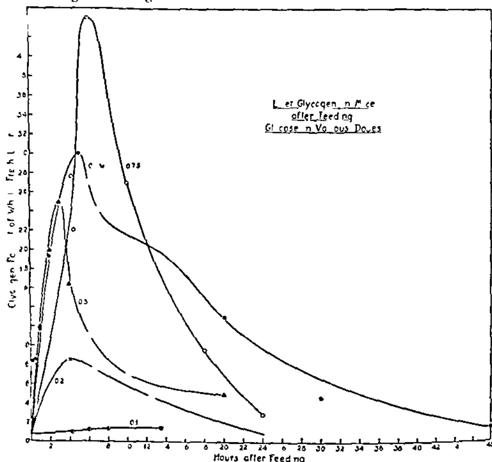


FIG 5 The figures attached to each curve indicate the grams of glucose fed per 100 grams of mouse For 0 7 gram both a winter and a summer curve are given After Salter W T Robb J D and Scharles F H Jour Nutrition 1935 IX 17

Storage of Ingested Glucose

Because various observers have disagreed as to the efficiency of absorption of glucose from the normal intestine Salter Robb and Scharles (1935) studied the formation of liver glycogen in mice after feeding various doses of glucose These data supplemented the earlier work of Cori (1926) who showed that the two processes of combustion and storage competed with each other Thus as shown in Figure 5 when

only a small dose of glucose was fed to fasting animals very little liver glycogen appeared because the sugar was burned as fast as it was absorbed. As the dose increased however the maximum concentration of liver glycogen was approached in about eight hours. Thereafter liver glycogen disappeared as the animals fasted longer.

The relative percentage of the fed glucose which finally appeared in the liver, however, was remarkably uniform as shown in Figure 6.

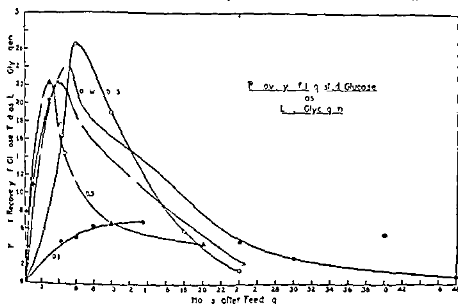


FIG 6. When glucose is ingested by mice the percentage which is transformed into liver glycogen is rather constant within the limits of dosage. After Salter W. T., Robb P. D. and Scharles F. H. Jour Nutrition 1935 IX 18

With the exception of the smallest dose studied which was largely combusted the other doses showed approximately the same relative contribution to the store of liver glycogen. This is the result which one would predict from a reversible mass law reaction but was hardly to have been expected in as complicated a system as the intact animal. It has been shown however by Trimble and Carey (1931) that after abundant feeding of sugar this material diffuses widely throughout body fluids so that high concentrations may be detected temporarily in the skin which acts as a sort of sponge or tampon reservoir. Obviously one is dealing in the postabsorptive stage with a very complicated problem and it is extraordinary that one can make any use at all of sugar tolerance curves to study disease as described in a later section.

cope with. Consequently 100 grams of glucose administered by mouth elevates the blood sugar curve no more than 15 grams placed by intubation directly into the duodenum. Levulose causes distinctly less elevation than glucose or galactose.

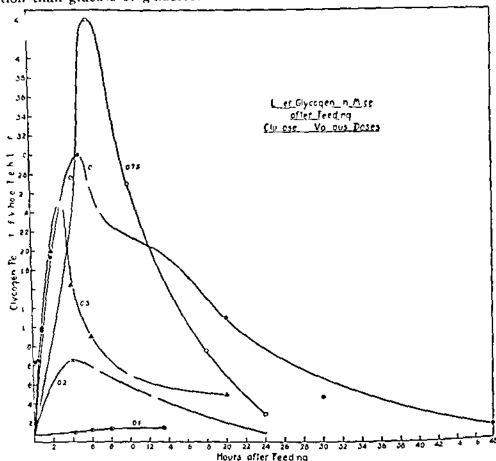


Fig 5 The figures attached to each curve indicate the grams of glucose fed per 100 grams of mouse. For 0.5 gram both a winter and a summer curve are given. (After Salter, W. T., Robb, E. D., and Scharles, F. H.: Jour. Nutrition 1935, IX, 17.)

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thyroid artificially it was found that the enzymic activity was quite different from that of the control animals and changed in a reverse direction after the feeding of glucose as shown in Figure 7 This action of amylase and its influence through a hormone would serve to explain such slow trends in carbohydrate metabolism as might occur in chronic states The amount of enzyme and its rate of action however are not sufficient to explain rapid redistribution of carbohydrate stores within the body Soskin and his associates (1938) therefore regard the function of amylase as a sort of primitive sluggish regulation upon which more rapid transformation of sugar is superimposed In recent years possible mechanisms for the speedy storage and release of carbohydrate have been found in connection with the rôle of hexose phosphates as described in the section on carbohydrate catabolism which follows shortly

After the monosaccharides have been absorbed into the blood stream they are disposed of in one of three ways namely by storage by catabolism or by excretion

Stores of Body Carbohydrates

The blood of a normal man contains only 5 grams of glucose and his entire body fluids probably contain less than 50 grams Except for temporary elevations in sugar concentration after meals or after intravenous therapy the dissolved glucose constitutes a relatively unimportant reservoir If not burned in the tissues any surplus of sugar is stored rapidly as glycogen Because of its colloid nature this glycogen remains immobile behind cell walls as described in Part II Many forms of carbohydrate and its derivatives can be transformed into liver glycogen some of these were studied by Salter Robb and Scharles (1935) Thus fructose sorbitol dihydroxyacetone lactic acid glycerin and propylene glycol all yielded glycogen in the liver of the mouse Within certain limits when glucose was fed glycogen stored in the liver was proportional to the amount fed as shown in Figure 6 The respective rates at which glycogen accumulates in the liver may differ Cori (1926) found that fructose was converted into glycogen more rapidly than galactose and possibly faster than glucose It is probable that most carbohydrate material other than glucose its polysaccharides and mannose must be converted into liver glycogen before it is available for use or storage elsewhere It even seems likely that substances like glycerin must first form liver glycogen before they can contribute to muscle glycogen Thus the sequence of events would progress in this order blood glycerin liver glycogen liver glucose blood glucose muscle glucose muscle glycogen

Of course as starvation persists the stored liver glycogen is mobilized to meet continued tissue needs This phenomenon is shown in Figure 6 In this mobilization of liver glycogen two distinct processes are described The first is the rapid liberation of glucose studied by Cannon (1940) as part of the emergency reaction involving adrenin The second and slower phenomenon *involving the liver amylase was followed by Scharles Robb* and Salter (1935) These investigators measured simultaneously the activity of liver amylase the enzyme which splits glycogen, and also of the glycogen itself in the liver They found that amylase activity var

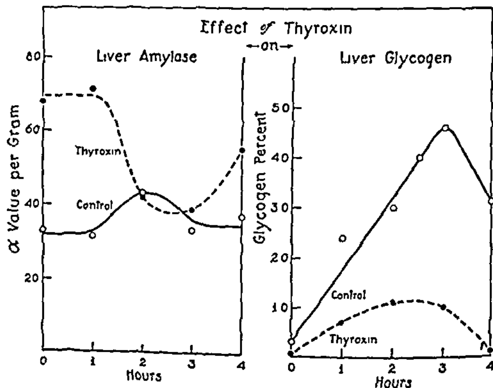


Fig 7 As glycogen is stored in the liver or paid out therefrom the glycogen splitting enzyme amylase also varies After Scharles F H Robb P D and Salter W T Am Jour Physiol 1935 CXI 134

ied widely with the nutritional state of the animal In general however the results suggested that an increased enzyme activity accompanied either the storage or the release of liver glycogen Again this is the result *which would be expected in view of the catalytic control which* the enzyme exerts over glycogen synthesis or glycogen breakdown Furthermore in animals treated with thyroxine and thus made hyper

various body structures was studied the series of values shown in Table IV expressed in percentage of fresh tissue was obtained

TABLE IV

	Maximum	Minimum
Liver	18 69	7 3
Muscle	3 72	0 [illegible]2
Heart	1 3	0 104
Bone	1 90	0 197
Intestines	1 84	0 0 6
Skin	1 68	0 09
Brain	0 29	0 047
Blood	0 [illegible]	0 0016

On the whole these figures represent unusually high concentrations In the discussion of carbohydrate in diet at the end of Part IV will be found standard values for the content of meat and other foods as ordinarily obtained As regards muscle meat from the steer however it may be noted that Moulton (1920) found in the muscle of a very thin steer 0 51 per cent of glycogen as compared with a value of 0 46 per cent in a very fat steer These values were computed after the fat had been removed from the meat otherwise they might have differed considerably because very fat meat may contain over 30 per cent lipoid Probably the highest concentrations of glycogen known are those found in von Gierke s disease The nature of this accumulation however is so evidently pathological that it will be discussed in Part V

Carbohydrate Catabolism

Although the synthesis of glycogen has been discussed in Part II it is chiefly through detailed studies of the degradation of glycogen in liver and in muscle that the chemical mechanisms involved have been elucidated The key to the unraveling of this complicated story which has puzzled biochemists for many years lies in the disclosure of the important rôles which phosphoric acid and its compounds play in connection with tissue carbohydrate metabolism Although it has been known for a long time that carbohydrate phosphate complexes were important in the biochemistry of muscle until very recently it had been assumed that changes in liver glycogen were due solely to the amylase previously described Nevertheless it seemed hard to understand how the trifling concentrations of this starch splitting enzyme found in tissues could account for the rapid fluctuations in liver glycogen known to occur under

Concentration of Tissue Carbohydrates

The concentration of carbohydrate stored in the body ordinarily is thought of in terms of the glycogen content. Obviously the extent of this accumulation depends upon many factors, i.e. dietary, hormonal and neuromuscular. For example Dudley and Marrian (1923) found that insulin convulsions in rabbits could reduce the normal liver glycogen from 5.5 per cent to 1.9 per cent and that of skeletal muscles from 0.6 to 0 per cent. Similar experiments by Best, Hoet and Marks (1926) showed that denervation of the skeletal muscles prevented this drop. Thus the glycogen in the tibialis fell to 0.01 per cent under the influence of insulin although the contralateral denervated muscle remained at 0.7 per cent.

Although the liver glycogen ordinarily is exhausted by a three days fast, muscle glycogen remains in considerable concentration after many days without food. For example Junkersdorf (1921) found in the dog that on the eleventh day of fasting the liver might still contain 1.6 grams of glycogen at 0.6 per cent and the skeletal muscles 6.6 grams of glycogen at 0.2 per cent. The same author also fed dogs a mixed diet corresponding to a standard human dietary. In Table III are given average analyses for several tissues.

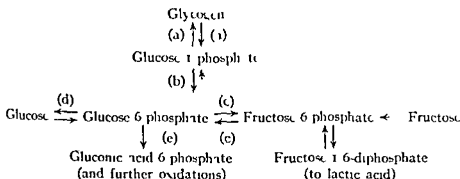
TABLE III

	Weight (grams)	Per Cent of Body Weight	Glycogen Content		
			Of Organ (%)	Average in Organ (grams)	Maximum in Organ (grams)
Muscle	3130	31.3	0.55	17.2	24.4
Heart	79	0.79	0.47	0.37	0.37
Liver	270	2.7	6.1	16.5	18.8
Kidney	47	0.47	0.15	0.07	0.07
				34.1	43.6

After Lusk, G. The Elements of the Science of Nutrition, p. 321, W. B. Saunders Company, Philadelphia, 1928.

In contrast to these values in the fasting state and under ordinary dietary conditions are the higher figures found after a diet rich in carbohydrate. Many years ago Schondorff (1903) gave seven dogs a high carbohydrate diet for nearly a week and then analyzed their tissues for glycogen content. The total glycogen in these animals ranged from 0.76 to 3.79 per cent. When the apportionment of glycogen throughout the

with muscle brownish with heart and reddish with brain In this connection it may be recalled that Young (1937A) has described a purified muscle glycogen preparation which gave a brownish to reddish violet color In brief the transformation of glycogen into Cori ester and also the reverse synthetic reaction can be demonstrated readily in the test tube A schematic representation of these several interrelationships has been given by Cori (1940) (see Diagram XIX)



Enzymes (Where no letters are given enzymes have not been named)

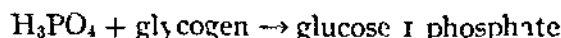
(a) phosphorylase (b) phosphoglucomutase (c) isomerase (d) phosphatase (e) glucose 6 phosphate dehydrogenase (Zwischenferment of Warburg) After Cori C F Endocrinology 1940 XXVI 291

In Diagram XIX two features are of especial interest First the phosphorylation of glucose and fructose indicated by broken arrows probably requires the simultaneous occurrence of a complex oxidation process this so called coupled reaction supplies the energy for the phosphorylating mechanism The other reactions occur without the actual presence of oxygen or without simultaneously occurring oxidation Second the reaction indicated by (d) occurs in liver Unlike muscle liver contains an enzyme phosphatase which converts hexose mono phosphate into glucose and free phosphate Herein lies the explanation for the fact that under physiological conditions liver glycogen may be transformed into blood sugar whereas muscle glycogen yields only lactic acid As indicated in Diagram XIX the combustion of carbohydrate may occur at the stage marked (e) through the mediation of the yellow enzyme system of Warburg and Christian (1937) Ordinarily this reaction may account for only a small part of carbohydrate combustion The main pathway of carbohydrate catabolism probably proceeds through

conditions of physiological stress The key to this dilemma was discovered by Cori Colowick and Cori (1938) who found that when glycogen and inorganic phosphate buffer were dissolved together in aqueous extracts of various organs e g of liver or muscle nothing happened until a trace of muscle adenylic acid described in Part II, was added Thereupon a rapid breakdown of the glycogen occurred

Glycogen Breakdown

The enzyme which initiates this degradation of glycogen occurs widely in animal and plant tissues Its action depends upon the cooperation of the coenzyme adenylic acid i e adenine ribose 5 phosphoric acid The reaction involved is a reversible one which accounts either for the first stage of glycogen breakdown or the final stage of its synthesis The reaction describing the formation of this Cori ester" may be written as follows



$$H_3PO_4 + \text{glycogen} \rightarrow \text{glucose 1 phosphate}$$

Particularly important is the fact that this enzyme is inactivated by phlorhizin a point which will be referred to again in connection with phlorhizin diabetes

The next step in the reaction consists in the transformation of the Cori ester to the Robison ester i e glucose 6 phosphate (see Part II under storage and fixation of small carbohydrate molecules) The enzyme which guides this reaction is known as phosphoglucomutase i e an enzyme which transmutes the phosphate attached to the glucose The reaction velocity is enhanced by magnesium ions

In tissues there is present yet another enzyme known as Lohmann s isomerase which speeds up the transformation of the glucose 6 phosphate into the so called Neuberg ester Thus in most tissues these two phosphate esters are present in equilibrium Their mixture is known as the Embden ester which is found normally in muscle When tissue extracts are allowed to act on glycogen all of the sugar involved is transformed into this Embden ester except in the case of liver to which we shall refer presently

Cori Colowick and Cori (1937) have been able to prepare synthetically large quantities of glucose 1 phosphate which they had identified previously as existing in muscle extracts When extracts of tissues are added to such a solution a rapid synthesis of a polysaccharide indistinguishable from glycogen occurs in vitro Moreover the product formed in each case gives a characteristic color reaction with iodine i e blue

It will be noted that the degradation of hexose is catalyzed by the coenzyme and that up to a certain point the process is essentially the same for both alcoholic fermentation and muscular activity How this latter process differs from the former can now be outlined in the following paragraphs

Biochemistry of Muscle

The pioneer work of Hopkins and Fletcher (1907) in the first decade of this century established the fact that muscular activity intimately involved changes in carbohydrate metabolism For many years thereafter in many parts of the world measurements were made of the lactic acid produced when muscle contracted anaerobically because it was believed that the evolution of energy and the actual shortening of the muscle fiber were connected directly with lactic acid In the last decade however due to the development of our knowledge of the compounds containing the phosphate radical the former concept has changed considerably

Although the precise details of the chemical and physicochemical machinery operating in contracting muscle remain obscure we now discern three cyclic processes which bear a certain analogy to the geared wheels in a clockwork These cycles are (1) the phosphocreatin cycle (2) the adenylic acid cycle and (3) the pyruvic lactic acid cycle As we understand muscular contraction at the present time an explosive release of energy in cycle (1) occurs concomitant with the release of free creatine and free phosphoric acid or phosphate This reaction appears to be the dominant one and it occurs independently After the energy stored in this cycle has been released this part of the system must be recharged in order to be effective again This reloading is accomplished by cycle (2) which interdigitates with the first cycle through the mediation of phosphate The key reaction through which these two cycles intermesh is probably the reversible Lohmann reaction in which adenyl pyrophosphate in cycle (2) reacts with the creatine released by the explosion of cycle (1)

Adenyl pyrophosphate + 2 creatine — adenylic acid + 2 creatine phosphate

This second cycle is analogous to an intermediary gear wheel in a clock work because apparently it simply transmits the energy rather slowly evolved in the third cycle which we call the lactic acid pyruvic acid cycle Again phosphate serves as the intermediary through which this interaction takes place The key reaction probably is the following

the Harden-Young ester, i.e. fructose 1,6-diphosphate to lactic acid as described in Diagram XIX

Alcoholic Fermentation

In the first decade of this century Harden and Young (1909) initiated a series of researches on the mechanism of alcoholic fermentation which have proved to be of great scientific importance not merely in their own right but also have led to a much better understanding of the chemical processes which go on in muscular activity. Out of their work came the recognition that carbohydrate metabolism involves two important types of compound which have been described already in this chapter. The first of these is the phosphoric ester or rather esters of glucose or fructose just described. The second is coenzyme I or cozymase the formula for which is related to coenzyme II as given in Diagram XVI. Due to the work of Neuberg (1918) and of Embden and his associates (1933) it has been possible to formulate the series of reactions involved in this process.

In brief form it may be stated that Harden and Young (1909) opened a fruitful field by finding that when sugars were fermented by yeast the addition of phosphate accelerated the fermentation. From this beginning came our understanding of the Harden-Young ester and the series of interrelated hexose phosphates just described in Diagram XIX. Later this process was extended by Meyerhof and his associates (1933) to include the triose phosphates which are intermediary between the hexose esters and alcohol. Meyerhof separated the chain of chemical events into two phases which may be sketched as follows. In the initial phase hexose diphosphate is transformed successively into triose phosphate, phosphoglycerate, pyruvate and acetaldehyde. In the second or stationary condition acetaldehyde is transformed successively into triose phosphate and into alcohol. To describe this chain of reactions accurately would require a series of complicated balanced equations which need not concern us here. In addition one would have to introduce a series of enzymes and coenzymes including the metallic ions of magnesium or manganese. In fact Warburg and Christian have expressed this complicated mechanism in terms of enzyme systems dealing with oxidation and reduction (1936). In particular they showed first that coenzyme I was needed to convert hexose monophosphate into pyruvate plus phosphoglycerate plus reduced coenzyme I. This reduced coenzyme also was involved in the conversion of acetaldehyde into alcohol plus coenzyme I (oxidized form).

DIAGRAM XX

I Glycogen + 2 H_3PO_4 —phosphorylase→ 2 hexosemonophosphate

II 2 hexosemonophosphate + adenylpyrophosphate —phosphorylase→ 2 hexosediphosphate + adenylic acid (+ 24 000 gm cals)

III 2 hexosediphosphate —zymohexase→ 4 triosephosphate (– 28 000 gm cals)

IV 4 triose phosphate + 4 pyruvate —mutase / coenzyme I→ 4 phosphoglycerate + 4 lactate (+ 32 000 gm cals) + c 24 000 gm cals)

V 4 phosphoglycerate —enolase→ 4 phosphopyruvate (± 0 gm cals)

VI 2 phosphopyruvate + adenylic acid —phosphorylase→ 2 pyruvate + adenylpyrophosphate (– 7400 gm cal)

VII adenylpyrophosphate + 2 creatine —phosphorylase→ 2 creatinephosphate + adenylic acid (+ 1000 gm cals)

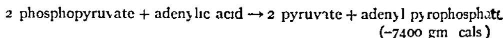
VIII 2 phosphopyruvate + adenylic acid —phosphorylase→ 2 pyruvate + adenylpyrophosphate (– 7400 gm cals)

Modified from Needham D M Perspectives in Biochemistry p 211 Univ Press Cambridge 1937 and Green D E pp 180–181 Univ Pres Cambridge 1937

Meyerhof (1932) has suggested that the interaction between the triose and hexose stages may be even more complex than is shown here but these details must be left to be explored in monographs which are strictly biochemical in character

It need only be added that this series of complicated reactions so nicely *intermeshed could not possibly maintain its smooth and rapid* coordination without the catalyzing effect of many enzymes which serve to guide its progress by accelerating processes which in vitro would proceed at a very slow rate

Biochemistry of Tumor —A special problem in carbohydrate catabolism *which has excited great interest and much work is the production* of lactic acid from glucose by tumor tissue Otto Warburg (1926) laid the groundwork in this field but many contributors following the work of


2 phosphopyruvate + adenylic acid → 2 pyruvate + adenyl pyrophosphate
(−7400 gm cals)

Thus in the third cycle glycogen breaks up to form the Harden Young ester described earlier in this section This hexose diphosphate then splits into two molecules of triose phosphate which on reaction with pyruvic acid yield phosphoglyceric acid and ultimately phosphopyruvic acid This last compound is the link which reacts with the adenylic acid of the second cycle

It is evident that in this process the slow transformation of glycogen into lactic acid is crudely analogous to the slow unwinding of the main spring and its associated pinion wheel of the clockwork The product of this degradation of glycogen is lactic acid and in the absence of oxygen this lactic acid gradually accumulates as the glycogen breaks down Careful quantitative studies of this relationship from the standpoint of energetics have been made by the school of A V Hill (1932) It is clear however that in the absence of oxygen lactic acid may continue to accumulate to a considerable extent and is a measure of the so-called oxygen debt to be described in Part IV It is also a measure of physical fatigue Even though an abundant supply of muscle glycogen still exists the muscle will become fatigued and eventually will fail to contract if the accumulation of lactic acid is not removed This removal can occur in two ways and both ways presumably operate Of five molecules of lactic acid so formed in the absence of oxygen one molecule is burned when oxygen becomes available and the other four are reconverted to glycogen Under ordinary conditions however there is presumably a steady breakdown of glycogen and an almost equally rapid oxidation of lactic acid so that very little of the latter accumulates

In this way glycogen supplies the energy for muscular contraction but only in an indirect fashion The chemical energy stored in the glycogen serves to activate cycle (2) which in turn charges the highly unstable cycle (1) The precise details of this series of reactions involve such a complicated series of interactions and dismutations that it is possible to give only the barest synopsis here Some of the reactions presumably involved are listed by Dorothy Needham in Diagram XX

Many of the reactions listed in Diagram XX as single simple transformations actually involve two or more stages but it will be apparent from a study even of these simplified equations that there is a reduplication of its members e g VI and VIII This is another way of expressing the cyclic character of the processes involved In addition the equations list tentative values for the energy released at each step Work by

to be oxidized contains only three carbon atoms it cannot be asserted with confidence precisely how this oxidation occurs For the present purposes probably it will suffice to suggest that in the presence of the appropriate enzymes coenzymes oxygen donators and hydrogen acceptors described by Dixon (1937) some such sequence of events as the following may occur

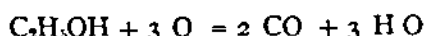
Lactic acid + oxygen = pyruvic acid + water
Pyruvic acid = acetaldehyde + carbon dioxide
Acetaldehyde + oxygen = acetic acid
Acetic acid = formaldehyde + carbon dioxide
Formaldehyde + oxygen = formic acid + water
Formic acid + oxygen = carbon dioxide + water

At best however this is a tentative scheme

In addition as indicated earlier in this section oxidation from glucose may occur at the longer chained stages Thus gluconic acid may be formed as shown in Diagram XIX through the intermediation of the yellow enzyme of Warburg and Christian (1936) Subsequently four carbon compounds related to succinic acid may be formed as suggested by Szent Gyorgy and described in Volume I Chapter V Already it is known that such oxidations are dependent upon coenzymes which involve the vitamins including nicotinic acid derivatives This story however falls outside the scope of the present chapter

Influence of Carbohydrate upon the Respiratory Quotient

Because the history of diabetes and investigations thereof past and present so often concern the respiratory quotient it is appropriate to note here that this metabolic index is primarily a manifestation of the properties of molecules and does not in itself imply vital processes Although originally described as the volume of carbon dioxide appearing in a given time divided by the volume of oxygen consumed in the same time the true implication of the quotient is a molecular one because of Avogadro s law For each molecule of oxygen consumed how much carbon dioxide is produced? This is the real import of the respiratory quotient and for this reason the respiratory quotient can be predicted precisely from balanced chemical equations Thus when alcohol is burned completely the respiratory quotient is 2 – 3 or 0 667 because the equation is as follows



$$C_2H_5OH + 3\ O\ = 2\ CO\ + 3\ H\ O$$

Thus two molecules of carbon dioxide were produced when three

Meyerhof (1927) on skeletal muscle have worked similarly on the peculiar behavior of malignant tissue in its utilization of glucose These observations have been summarized critically by Burk (1937) who has pointed out their relation to fermentation or as Pasteur described it, la vie sans air In brief tumor tissue like embryonic tissue is capable of fermenting glucose to lactic acid in the absence of oxygen Unlike embryo however tumor tissue seems to prefer to ferment even when oxygen is available Consequently in a given time tumor tissue uses up about as many calories by fermentation as it does by oxidation and in this process destroys some twenty times its dry weight per hour in glucose It seems likely that this tendency to fermentation is related to a lack of the usual enzyme systems which in normal cells bear the brunt of oxygen activation For example Craig Bassett and Salter (1941) have found tumor tissues of various histological types to be deficient in cytochrome system activity which normally carries over 90 per cent of the traffic of combustion Furthermore Kensler Sugiura and Rhoads (1940) have found that another interference with oxidation enzymes occurs in liver tumors induced by feeding the carcinogenic dye butter yellow

It has been shown by Cori and Cori (1925A 1925B) that this abnormal lactic acid production occurs in the naturally growing tumor Indeed attempts have been made to have the tumor destroy itself through excessive accumulation of this metabolite Such attempts however have merely induced extensive necrosis of the tumor without completely destroying the outermost shell of viable tissue

As pointed out by Burk (1939) this abnormal carbohydrate metabolism may not be completely specific for malignant tissue It seems to be related to rapid growth and to deficiencies or injuries involving enzyme systems concerned with oxidation Indeed the pure scientist looks upon it as a natural experiment which offers a clue to the understanding of the mechanism by which normal cells consume their fuel The therapeutic experimentalist however still hopes that in this abnormal metabolism there may lie a vulnerable function through which malignant tissue may be destroyed without destroying normal cells elsewhere in the body

Combustion of Carbohydrate

It is clear from the comments on the accumulation of lactic acid just described that eventually oxidative processes must intervene or else the constant release of energy from carbohydrate stores will slow down and cease Strangely enough although the substrate (lactic acid)

mated effect of many heterogeneous reactions occurring simultaneously In short there is nothing very specific about the value and for this reason its interpretation must be formulated with great caution

While recognizing the nature of these average values the R Q has nevertheless been used with considerable practical advantage in the study of metabolism For example in the indirect method of calorimetry it is often sufficiently accurate to assume that in the basal state the average nonprotein R Q value for a relatively healthy individual is about 0 85 Furthermore by assuming a certain basal protein consumption an average fasting R Q value of 0 82 can be used satisfactorily in the clinic when basal metabolism is determined solely from the rate of oxygen consumption At best however these values represent only convenient assumptions As already pointed out in Part II it is probable (Ashford and Holmes 1931) that the brain burns carbohydrate almost exclusively so that its R Q is always close to 1 0 Accordingly there must be other processes with a very low value going on simultaneously to produce the gross average of 0 83 mentioned above

As will be discussed later in connection with diabetes mellitus the respiratory quotient characteristically found in this condition when severe may be close to 0 68 In former times this value was interpreted to mean that the organism in diabetes burnt fat almost exclusively Although it is true that such an organism is consuming large amounts of fatty acid and protein there is good evidence reviewed in the next section that diabetic animals and patients burn a considerable amount of carbohydrate Accordingly the low R Q found in these individuals is probably the net result of two components (a) the low R Q resulting from gluconeogenesis i e the formation of sugar from protein and fatty acid stores and (b) the high R Q produced by the concomitant oxidation of such newly formed carbohydrates

There is a complicating technical effect in the determination of R Q value which must always be borne in mind because it constantly plagues investigators in the laboratory and in the clinic This is the blowing off of carbon dioxide from the blood buffer and tissue fluids Such carbon dioxide must be regarded essentially a being a structural component of the organism in a steady state and if it is released temporarily equivalent amounts must be retained subsequently to compensate In this way an excited breathless individual may yield an R Q of 0 9 in the first hour of observation and an R Q of 0 5 in the second hour when the individual has resumed equanimity These fluctuations have no nutritional significance the individual s true R Q value due to combustion was close to 0 7 during the entire period When confronted with unusual values for carbon dioxide production particularly in determining the metabolism of children the clinician must bear this source of error in mind

molecules of oxygen were consumed According to Avogadro s law this would mean that three volumes of oxygen measured at normal temperature and pressure disappeared while two volumes of carbon dioxide also measured at normal temperature and pressure appeared Similarly the crude overall equation for the oxidation of glucose indicates that equal volumes or molecular equivalents of oxygen and carbon dioxide are concerned $C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O$ In short the R Q equals 6 divided by 6 or 1 00 When similar equations are written for mixed proteins the value derived is about 0 82 On the other hand for pure neutral fat it is 0 71

The respiratory quotient compares only the initial intake of oxygen in a chemical process with the final output It gives no inkling as to the intermediary mechanisms involved When a number of heterogeneous reactions are taking place it reflects only the net balance between oxygen and carbon dioxide Although hydrogen is seldom mentioned in connection with the R Q of biochemical processes this element is the controlling factor in the value obtained This is true because when oxygen is diverted for the oxidation of hydrogen (to form water) the R Q drops and less carbon dioxide appears per molecule of oxygen utilized

The following examples will explain this further First when fatty acid which contains very little oxygen is burned a great deal of oxygen is needed to consume the hydrogen in the molecule For example if stearic acid is burned completely the resulting equation describing the overall process is $C_{17}H_{35}COOH + 26\ O_2 = 18\ CO_2 + 18\ H_2O$ It is obvious that the respiratory quotient resulting from this reaction would be near 0 69 i e 18 divided by 26 because so much oxygen was used in the combustion of hydrogen

Second very low quotients may result from the partial oxidation of food stores when the carbon therein remains unburnt Thus when fat is changed into glucose oxygen is incorporated into the organic molecule without yielding carbon dioxide For example in the case of the fatty acid $C_{17}H_{35}COOH$ three molecules of glucose amounting to 18 C + 36 H + 18 O are formed This new formation of glucose i e gluconeogenesis from fatty acids has required the fixation of several molecules of oxygen without the liberation of any carbon dioxide Accordingly the respiratory quotient for this single chemical step would be 0 0 or zero Actually the natural store of fat in the animal body consists of glycerol esters of such fatty acids and this glycerol radical might be burned when the fat is changed into sugar Such a process would raise the net R Q to about 0 2 From what has been said therefore it is obvious that the respiratory quotient as obtained in a living mammal represents the composite sum

possible basis for such disturbances as a prelude to the consideration of von Noorden's (1927) overproduction theory of diabetes to be discussed in the next section

Antiketogenesis —The fact that the burning of sugar derived either from glycogen or from part of the protein molecule prevented the development of ketosis has long been known and the fact remains well substantiated Formerly however it was supposed that the ketone bodies were toxic products resulting from the incomplete oxidation of fatty acids This hypothesis was the basis of the flame of the carbohydrate philosophy With the rise of the overproduction theory however an alternative interpretation came to challenge the former theory This newer view was that the fat stores in the body could be transformed into sugar and other foodstuffs of small molecular size and that the ketone acids represented individual stages in this chemical process The gluconeogenesis from fat was regarded as a normal nutritional mechanism which caused trouble in the diabetic individual simply because the rate of gluconeogenesis from fat and from certain amino acids became excessive According to this viewpoint the accumulation of ketone bodies was analogous to the dumping of goods upon a satiated market in the economic sphere This overproduction of foodstuffs involved glucose as well but the sugar largely escaped through the urine without producing obvious immediate damage The ketone bodies however being moderately strong organic acids depleted the body reserve of base and the buffer capacity of the body fluids Consequently the organism became progressively acidotic In brief the production of fuel had exceeded the rate of consumption although the latter rate remained fairly normal

A large body of evidence has been accumulated in support of this latter point of view so large that it formed the basis of a monograph by the late J J R Macleod (1928) It must suffice here to note a few interesting experimental facts which are not easily reconciled with the older conception of the acetone bodies as abnormal toxins For example several investigators have showed that in the Eck fistula cat whose liver gradually diminishes in size (Ring and Hampel 1933) the removal of the pancreas may produce mild diabetes but very little ketosis Much more evidence implicating the liver as the source of the ketone bodies will be presented in the next section More cogent was the work of Chaikoff and Soskin (1928) who studied the usefulness of acetone body as a food These investigators injected into dogs solutions of sodium acetoacetate and studied the rate at which such material could be utilized They found that if the dog had neither liver nor pancreas this reduced animal could use acetone body as readily as normal animals When the

Influence of Carbohydrate on the Metabolism of Other Foodstuffs

In Volume I, Chapter V, mention was made of the isodynamic law of Rubner (1902) which stated that the three foodstuffs, carbohydrate, protein and fat, could be used interchangeably as fuel in the animal organism provided substitutions were made in accordance with the respective caloric equivalents of the fuels concerned. This law is the basis of modern dietetics and needs no further comment here. There are highly significant limitations, however, to the application of the principle. First, as pointed out in Volume I, Chapter V, there is a minimal protein requirement which may not be transgressed if body protoplasm is to be preserved. Second, the carbohydrate contribution to the fuel being consumed may not be reduced too far lest ketosis and acidosis result. Strictly speaking, this second restriction concerns all of the so-called "antiketogenic" moiety of bodily fuel, which is made up not only from the carbohydrate but also from the antiketogenic portion of the protein metabolism, namely, about 58 per cent of the protein which is burned.

For nearly a generation it has been stated that "fat is burned in the flame of the carbohydrate," and the Woodyatt ratio (1916) has formed the basis of diabetic diets and, indeed, of all diets. The basic observations upon which this philosophy was founded remain unchallenged, but their interpretation now appears crude in the light of modern studies. Such clinical observations as those of Stadie (1940) will be cited in a subsequent section in discussing modern views on diabetes and ketotic acidosis. Meantime it must be explained that a new concept of carbohydrate metabolism has developed. This concept is that there exists a dynamic equilibrium involving blood sugar (glucose) resulting from two opposing trends. The first of these trends is the formation of blood sugar by the liver. The second is the utilization of that sugar by the body tissues. In the nondiabetic organism the rates at which these two processes occur are equal, and the blood sugar remains constantly at a normal level without any complicating loss through glycosuria and without the development of ketosis. When a discrepancy in these two rates occurs within certain limits the organism is able to compensate. For example, it will be pointed out in Part V that in the insulin-insensitive organism a rise in the blood sugar level speeds up the burning of sugar in the tissues, and for a time the individual enjoys essentially normal carbohydrate balance at a relatively hyperglycemic level. In extreme cases, however, this compensation breaks down and consequently the several characteristic disturbances of diabetes occur. Let us review the

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possible basis for such disturbances as a prelude to the consideration of von Noorden's (1907) overproduction theory of diabetes to be discussed in the next section

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liver remained intact however the depancreatized animal produced large quantities of the acetoacetate spontaneously along with large amounts of glucose In short both the ketosis and the glycosuria depended upon the action of the liver Likewise Embden and Lattes (1908) showed that the livers of phlorhizinized or depancreatized animals yielded more acetone body than did the livers of normal animals In addition Mirsky and Broh Kahn (1937) have shown that the ease with which beta hydroxybutyric acid is disposed of by tissues other than the liver bears no relation to the amount of sugar being burned by these tissues Therefore it is no longer possible to be content with the old 'flame of the carbohydrate aphorism Rather it seems likely that the acetone bodies represent a normal intermediary stage between fatty acid and sugar Indeed Weil Malherbe (1938) has suggested that slices of kidney tissue in vitro can produce sugar from acetoacetic acid

Gluconeogenesis — The large excretion of sugar in the urine of diabetic individuals was interpreted formerly as indicating an inability of the organism to oxidize glucose Although it still is conceded that the diabetic individual may suffer from a moderate diminution in his capacity to burn sugar it now appears that the high sugar excretion is markedly out of proportion to this slight handicap For a long time it was presumed that the urinary sugar was drawn from two sources only namely from body stores of glycogen and from body protein As evidence of the latter source have been cited many measurements of the D N ratio which since the days of Minkowsky (1893) had been interpreted as showing that a constant proportion of protein was transformed into glucose and that this entire moiety was excreted in the urine because the tissues were nearly totally unable to burn sugar Soskin (1940) has pointed out however that this D N ratio is by no means constant in completely depancreatized dogs and that relatively less glucose is excreted in relation to nitrogen as the diabetes progresses Furthermore fat dogs excrete more glucose per gram of nitrogen than do thin dogs Such observations have suggested that much of the urinary sugar excreted by diabetic animals represents body fat which has been mobilized and partially oxidized As time has gone on more and more convincing evidence has accumulated that the body fat is mobilized in the diabetic animal that it travels through the blood stream to the liver and that the liver transforms it first into ketone bodies and then into glucose The evidence is complicated but has been reviewed by Macleod (1928)

In the light of this newer evidence several classical clinical observations in severe diabetes become readily explicable The rapid mobilization of body stores accounts for the wasting of the patient s muscles

and adipose tissue so characteristic of the young severe diabetic The lipemia of severe diabetes also indicates that there is a tremendous traffic of fat from body stores to the liver The fatty infiltrated liver of the patient dying in coma is further evidence of this traffic From this standpoint it is easy to understand why the patient with severe diabetes excretes almost quantitatively any sugar which may be administered He is already producing more than he needs and any further addition simply is excreted in toto It still remains to be learned why the diabetic organism throws out its food reserves in such a wasteful and extravagant fashion Already however there are inklings that normally this regulation is the function of the hormones which to be sure were long ago termed the regulators of metabolism In short as will be described in Part IV diabetes mellitus is coming to be regarded not merely as a pancreatic defect but rather as an example of altered imbalance among several endocrines

March 1 1942

PART IV

NUTRITION AND CARBOHYDRATE

FLUCTUATIONS IN CARBOHYDRATE BALANCE

Until a decade ago carbohydrate balance was thought of chiefly as the difference between the rate of intake and the rate of combustion. Diabetes mellitus, for example, supposedly was due solely to an inability of the tissues to oxidize glucose. Except for the concept of the liver as an emergency reservoir for easily available carbohydrate, it was supposed that carbohydrate balance was not influenced specifically by any special organ or group of organs. The chief exception to this statement was, of course, pancreatic diabetes. Beginning with the work of Houssay and his collaborators (1936), however, a large body of evidence has accumulated to show that carbohydrate balance is connected intimately with endocrine balance. It is important, therefore, to consider two main aspects of the problem of carbohydrate nutrition, namely (1) the effect of hormones in controlling the distribution of carbohydrate throughout the organism and (2) the ultimate net effect of carbohydrate combustion and storage within individual organs.

EFFECT OF HORMONES

As might have been anticipated, the development of this newer point of view with regard to carbohydrate metabolism centered about observations as to the mechanism of diabetes mellitus. Out of the many and complex findings of Houssay and his collaborators the following fact was the most striking which emerged. Although a dog dies in diabetic coma soon after the removal of his pancreas, the animal will survive for a long period if, in addition to the pancreas, the pituitary gland also is removed. In short, the loss of two organs proves less nocuous than the loss of a single one. Houssay established many interesting supportive and contributory observations which emphasize the primary finding. For example, after hypophysectomy alone the animal becomes much more sensitive to a given dose of insulin, and contrariwise, the parenteral administration of extracts of the anterior pituitary lobe diminishes the sensitivity to insulin as measured by the fall in blood sugar. Likewise the administration of anterior pituitary extracts to normal animals can produce a condition closely resembling pancreatic diabetes. Since these original findings were made a great deal of work has been devoted to the

elucidation of the mechanisms involved As will emerge presently from the discussion this is not a simple problem because the pituitary influences the activity of other glands of internal secretion, which are involved in the maintenance of carbohydrate balance Thus the adrenal cortex and medulla the thyroid and the pancreas all are known to be concerned in the homeostasis of glucose to use Cannon s term (1929)

At least two of these hormones namely the thyroid and the adrenal cortex are controlled specifically through their respective tropic hormones from the anterior pituitary In addition it is suspected that there may be also a pancreotropic factor in pituitary extracts as stated by Anselmino Herold and Hoffman (1933) although this is not yet established The problem is complicated further by the probability that the anterior lobe secretes one or more principles which affect directly carbohydrate metabolism in the general body tissues In addition it has long been known that the posterior lobe of the pituitary or at least extracts therefrom exert an effect antagonistic to insulin In discussing this complicated maze of possible actions and interactions it will be necessary to consider one factor at a time but it must be remembered constantly that in the animal these various factors are interacting with various possible combinations of compensation and overcompensation

Glycotropic Substance of Anterior Pituitary

The term glycotropic substance is applied to that action of the pituitary extracts which is concerned with the reduction of the effectiveness of insulin in the animal body Young (1938) has shown that it is not identical with the thyrotropic or gonadotropic hormones nor with prolactin It seems also to be distinct from the ketogenic factor in that it is more resistant to heat In normal animals this material is not in itself productive of diabetes although it well may be concerned in the mechanism of diabetes mellitus As shown by Benedetto (1933) when normal or hypophysectomized animals are treated with extracts containing this material they become relatively insensitive to a standard dose of insulin Because this action is without effect upon the resting blood sugar the material sometimes is known as the anti insulin factor or the glycostatic substance (Russell and Bennett 1936)

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Until a decade ago carbohydrate balance was thought of chiefly as the difference between the rate of intake and the rate of combustion. Diabetes mellitus for example supposedly was due solely to an inability of the tissues to oxidize glucose. Except for the concept of the liver as an emergency reservoir for easily available carbohydrate it was supposed that carbohydrate balance was not influenced specifically by any special organ or group of organs. The chief exception to this statement was of course pancreatic diabetes. Beginning with the work of Houssay and his collaborators (1936) however a large body of evidence has accumulated to show that carbohydrate balance is connected intimately with endocrine balance. It is important therefore to consider two main aspects of the problem of carbohydrate nutrition namely (1) the effect of hormones in controlling the distribution of carbohydrate throughout the organism and (2) the ultimate net effect of carbohydrate combustion and storage within individual organs.

Effect of Hormones

As might have been anticipated the development of this newer point of view with regard to carbohydrate metabolism centered about observations as to the mechanism of diabetes mellitus. Out of the many and complex findings of Houssay and his collaborators the following fact was the most striking which emerged. Although a dog dies in diabetic coma soon after the removal of his pancreas the animal will survive for a long period if in addition to the pancreas the pituitary gland also is removed. In short the loss of two organs proves less nocuous than the loss of a single one. Houssay established many interesting supportive and contributory observations which emphasize the primary finding. For example after hypophysectomy alone the animal becomes much more sensitive to a given dose of insulin and contrariwise the parenteral administration of extracts of the anterior pituitary lobe diminishes the sensitivity to insulin as measured by the fall in blood sugar. Likewise, the administration of anterior pituitary extracts to normal animals can produce a condition closely resembling pancreatic diabetes. Since these original findings were made a great deal of work has been devoted to the

The striking feature which emerges from this artificial diabetes is its resemblance in many respects to clinical diabetes In consequence laboratory experimenters have distinguished between pancreatic and pituitary diabetes and clinicians are separating insulin sensitive from insulin resistant patients In a later section will be discussed the use of glucose insulin tolerance curves for this purpose First however the action of other endocrine glands themselves under the influence of the pituitary must be considered In addition the pars posterior of the pituitary body itself must be mentioned

Posterior Pituitary — An influence of pituitrin upon carbohydrate metabolism has long been recognized although its mechanism remains obscure (Hines Leese and Boyd 1927) It tends to counteract the effect of insulin and indeed sometimes has been injected to relieve insulin reactions e g in children when the administration of glucose is difficult Its effect well may involve the formation of hexosephosphate because the serum inorganic phosphate tends to fall shortly after pituitrin is given This effect seems to be associated with the pitressin factor rather than with the oxytocic fraction

Thyroid — This important endocrine organ is under the tonic influence of the thyrotropic hormone which is secreted constantly by the anterior pituitary The results of its hormone have been studied extensively since the isolation by Kendall (1915) of the active principle thyroxine The actual mechanism of the thyroid effect in tissues is discussed in another section but the net result in the animal body may be summarized briefly here Under the influence of thyroxine the glycogen reserves in the liver are depleted rapidly and the storage of newly acquired glucose in the liver is interfered with Consequently although excessive oxidation of carbohydrate tends to keep the fasting blood sugar low immediately after the feeding of glucose or starch the blood sugar tends to rise with abnormal rapidity presumably because storage as liver glycogen is prevented The postprandial hyperglycemia may be so severe as to produce glycosuria and in the clinic the diagnosis of diabetes mellitus may be made tentatively In our present conception of sugar diabetes as a state of endocrine imbalance it is not clear that the hyperglycemia accompanying hyperthyroidism is essentially different from hyperglycemia occurring in classical uncomplicated cases of diabetes mellitus Much clinical effort is often expended in an attempt to differentiate the two syndromes Perhaps this is only wasted time The muscle glycogen usually suffers far less than liver glycogen but with the severe wasting of skeletal muscle which frequently accompanies severe Graves disease a considerable loss of this carbohydrate store may ensue In addition

anterior lobe extracts for a fortnight may produce remarkable changes in the pancreas of the rat without causing diabetes These changes which are found also in other animals include marked mitotic activity and increase in size of the islet tissue together with a concomitant increase in the insulin content of the organ Because this effect would tend to counteract the diabetogenic action of anterior pituitary extracts it seems possible that even in the direct action of the pituitary gland one may have to reckon with mutually opposing reactions

Diabetogenic Effect of Anterior Pituitary

Shipley and Long (1938) have suggested that a single pituitary principle conceivably may have three distinct effects namely (a) growth producing (b) ketogenic and (c) diabetogenic At present there is a tendency to attribute these respective effects to individual substances without good chemical evidence for separating them Thus when Burn and Ling (1930) reported the production of ketone bodies after the administration of anterior pituitary extracts they considered the possibility of a distinct ketogenic factor It is evident however that the diabetic state is a complex phenomenon and that probably the term diabetogenic simply records the net effect of a number of separate responses to anterior lobe extracts Among these would be included the depression of carbohydrate oxidation the inhibition of insulin secretion, the anti insulin action and the favoring of glycogen formation within liver and muscles The solution of this question awaits the production of pure pituitary principles by biochemists

There is no doubt that the prolonged administration of appropriate extracts of anterior lobe can produce a permanent state of diabetes in dogs as shown by Young (1937B) After several weeks of such treatment the ketosis so produced may become worse many months later Glycosuria continues in marked degree and heavy doses of insulin may be required to control it When the islands of Langerhans are examined in such animals there is found to be a loss of the cytoplasmic granules of the beta cells and in extreme cases extensive hyaline degeneration and even fibrosis Like diabetic patients these animals may improve remarkably on a high fat diet The precise nature of the colloidal substance which produces this permanent diabetes has not been determined Among the possibilities which have been excluded are the glycotropic gonadotropic and thyrotropic substances and the metabolism stimulating factor of Collip (1938) The ketogenic adrenotropic and anti insulin factors as yet have not been entirely eliminated

the confusing literature on this subject. Moreover there is already some clinical evidence that in certain patients with adrenal cortical pathology the electrolyte disturbance predominates, whereas in other patients a disturbance in carbohydrate balance may be more manifest. In normal and adrenalectomized dogs and rats Thorn, Engel and Lewis (1941) found that whereas desoxycorticosterone favored a positive sodium and chloride balance, compound E showed the reverse influence.

TABLE X

EFFECT OF CORTICAL EXTRACT ON THE DISPOSITION OF GLUCOSE IN THE RAT

	Fasted (1)	Glucose fed (8)	Glucose and cortical extract (10)
Glucose absorbed	—	756 ± 15	684 ± 19
Muscle glycogen	253 ± 15	393 ± 1	41 – 16
Extra muscle glycogen	—	140	159
Liver glycogen	± 1	135 5	1,8 ± 7
Extra liver glycogen	—	1 8	1,1
Glucose in body fluids	3	5	72 ± 5
Extra glucose	—	0	35
Urine nitrogen	14 0.6	13.6 ± 0.6	13.6 0.6
CO_2 (c.c.)	—	548 + 1	485 – 16
O_2 (c.c.)	—	635 ± 16	628 ± 1
R. Q.	—	0.851 ± 0.005	0.81 0.005
Non protein R. Q.	—	0.866 + 0.005	0.766 ± 0.005
Glucose oxidized	—	361 2	154 – 13
Total glucose recovered	—	649 ± 16	519 + 30
Per cent recovery	—	86 ± 1.8	76 ± 2.7

All values are expressed as mgm. per 100 gm. of body weight per 4 hours.
After Long, C. N. H., Katzin, B., and Fry, L. G., Endocrinology, 1940, XXVI, 3 0

Mason, H. L., Myers, C. S., and Kendall, E. C. (1936) have described the isolation of several adrenal steroids from the cortex of the gland.

Mobilization of Body Stores of Fuel

Long, Katzin and Fry (1940) have presented a great deal of evidence which indicates that the hormones of the adrenal cortex control the metabolism both of carbohydrates and of proteins. Among the several effects observed in this connection was the following: When cortical extracts were administered to fasting normal rodents or to adrenalecto

with the loss of natural mucoprotein which occurs in hyperthyroidism the opposite of myxedema a certain amount of carbohydrate is destroyed when the mucoprotein is released As pointed out in Volume I, Chapter V it is necessary to combat this excessive loss of glycogen in hyperthyroid patients through a high carbohydrate high caloric diet if extensive loss of body protein is to be avoided

Adrenal Medulla — The emergency reaction of Cannon (1932) is so well known that little comment need be made here upon the effects of adrenin Repeated prolonged exhibition of this hormone not only may deplete the liver glycogen but after extensive muscular activity may result in a definite decrease in the muscle glycogen as pointed out by Macleod (1934) Nevertheless the effect of this hormone usually is transitory under natural conditions and much of the lactic acid liberated from shivering muscles is trapped in the liver and resynthesized to glycogen Consequently serious disturbances in carbohydrate metabolism from this source occur but rarely in the clinic The unusual adrenal tumor medullary in type is a possible exception to this statement

Adrenal Cortex — Almost as revolutionary as the findings of Houssay were the subsequent observations of Long and Lukens (1936) and of their collaborators Working chiefly with cats which had been subjected to pancreatectomy these investigators noted that the resultant diabetes could be ameliorated remarkably by removal of the thyroid and particularly by removal of the adrenal cortex Until very recently such observations have been complicated by the marked disturbance in electrolyte balance which total removal of the adrenal cortex produces Many of the original observations on the carbohydrate metabolism of such animals or of patients in the clinic suffering from Addison s disease represented side effects accompanying an agonal decline Very recently however the isolation of a crystalline carbohydrate substance (compound E of Kendall) has served to clarify the situation well by enabling investigators to discriminate between the carbohydrate and electrolytic features of adrenal cortical insufficiency Although the whole truth awaits more elaborate study in what follows the assumption may be made without great error that the electrolytic effects of Addison s disease may be corrected by administering desoxycorticosterone acetate and are presumably due to a lack of this or similar chemical compounds The abnormal carbohydrate metabolism of Addison s disease on the other hand may be relieved by administering 17 hydroxy 11 dehydrocorticosterone the carbohydrate influencing steroid known as compound E The ability to separate these two effects of the adrenal cortex by the use of pure crystalline compounds with different physiological effects has simplified vastly

ycorticosterone has very little effect as compared with that of cortical extract or of crystalline corticosterone and 11-dehydro 17 hydroxycorticosterone

Cortical Hormone and Diabetes

Long and his collaborators were able to pry further into the intimate mechanism of diabetes by working with the Houssay animals described above It will be remembered that hypophysectomy relieved pancreatic diabetes Conversely it was found that adrenal cortical extract made it worse just as anterior pituitary extract does *Apparently a synergism* exists between the pituitary and adrenal hormones in this respect in that each reinforces and exaggerates the effects of the other Similarly as might be expected hypophysectomized animals suffering from profound hypoglycemia while fasting were greatly improved by the exhibition of cortical extract Under such circumstances the effect of low liver glycogen and low blood glucose was overcorrected and an increase in urinary nitrogen excretion occurred In connection with the overproduction theory to be discussed later it is of interest that the cortical hormone can stimulate the production of carbohydrate by breaking down protoplasmic stores of protein with the consequent excretion of unusual amounts of discarded nitrogen and potassium

The mechanism of the effect of cortical hormone upon tissue metabolism has been investigated further by Lewis Kohlman Delbue Koeph and Thorn (1940) and by Thorn and his collaborators (1940) who showed that in patients with Addison s disease cortical hormone had a striking effect on carbohydrate utilization as well as on gluconeogenesis i e the production of sugar from non carbohydrate stores Further investigation of the carbohydrate metabolism in adrenalectomized animals poisoned with phlorhizin showed (1) that these animals did not readily form glucose from lactic acid pyruvic acid or alanine (2) that they utilized available glucose to an increased extent and (3) that they showed a decrease in such characteristically diabetic phenomena as glycosuria ketonuria excretion of nitrogen and glucose nitrogen ratio These data are illustrated in Table VI

As might have been expected after removal of the adrenal from dogs the animals exhibited difficulty in mobilizing sugar when treated with adrenin or with insulin These results are demonstrated in Figure 9 Interestingly enough they likewise showed a decreased threshold for signs of hypoglycemia induced either by insulin or by poisoning with phlorhizin

mized rodents large increases in liver glycogen were found together with a slight hyperglycemia These results suggested that body protoplasm was mobilized to increase available fuel in the liver

The muscle glycogen was not affected unless the animals were fed After feeding muscle glycogen increased and ususually large quantities of glycogen accumulated in the liver The possibility therefore exists that in fasting animals tissue proteins may be mobilized to supply the extra carbohydrate while the nitrogen moiety is discarded and excreted The increased proportion of administered glucose stored as liver glycogen

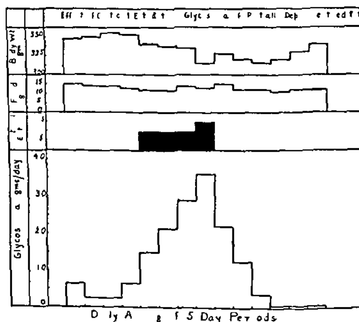


FIG 8 Effect of adrenal cortical extract on the glycosuria of a partially depancreatized rat After Long C N H Katzin B and Fry E G Endocrinology 1940 XXVI 329

in the treated animals apparently involved a diminished proportion of glucose oxidized These effects are illustrated in Table V Converse effects were obtained in adrenalectomized animals which when fasting showed subnormal muscle and liver glycogen and blood glucose

Of especial interest are the results reported by these investigators in partially depancreatized rats because such animals are on the verge of diabetes mellitus The glycosuria which results when these animals are treated with cortical extract or corticosterone is illustrated in Figure 8 Such diabetes can be relieved by removing the adrenal and then in these adrenalectomized animals intensified again by administering cortical hor mone As suggested earlier in this section the crystalline steroid, desox

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Cortical Hormone and Phlorhizin

The animals just described had been maintained with salt or with desoxycorticosterone acetate in order to keep their electrolytes within normal limits. In this way it was possible to separate out that portion of the symptomatology of Addison's disease artificially produced which is attributable to deranged carbohydrate balance. In such animals it was possible to follow the restoration of normal carbohydrate balance after treatment with 17 hydroxy 11 dehydrocorticosterone or with adrenal cortical extract.

TABLE VI

EFFECT OF ALANINE TREATMENT ON THE GLUCOSE NITROGEN RATIO OF ADRENALECTOMIZED PHLORHIZIN TREATED RATS

Animals used	Treatment	Glucose excretion	Nitrogen excretion	Glucose Nitrogen ratio
		mgm /100 gm /24 hr	mgm /100 gm /24 hr	
Adrenalectomized and phlorhizin treated (3)	None	148	64	3
Adrenalectomized and phlorhizin treated (4)	Alanine 1.0 gm	420	160*	2.6
Normal control phlorhizin treated (3)	None	488	13	3.7
Normal control phlorhizin treated (3)	Alanine 1.0 gm	670	04	3.3

* Nitrogen excretion refers to the total nonprotein nitrogen excretion from which the amino acid nitrogen excretion has been deducted.

After Lewis, J. A., Kuhlman, D., Delbue, C., Koepf, G. F., and Thorn, G. W., Endocrinology, 1940, XXVII, 975.

For example, in adrenalectomized animals poisoned with phlorhizin such therapy restored their ability to produce glucose from lactic acid, pyruvic acid or alanine; it also decreased the utilization of available glucose and increased the manifestations of diabetes such as ketonuria, glycosuria, nitrogen excretion and the characteristic primary glucose nitrogen ratio. It will be observed that this is a reversal of the effect of adrenalectomy already described.

Likewise such therapy raised the threshold for signs of hypoglycemia after treatment with insulin or with phlorhizin. These results are illustrated by the experiment shown in Figure 10. Further evidence of this diabetic trend in adrenalectomized dogs after the administration of corticosterone or adrenal cortical extract was the lowering of the respiratory

quotient an increased excretion of urinary nitrogen and an increase in the blood glucose concentration

These observations shed considerable light upon the mechanism whereby certain secretions of the adrenal cortex influence carbohydrate balance Such secretions are concerned intimately with the ability of the organism to convert the six carbon glucose and its storage product

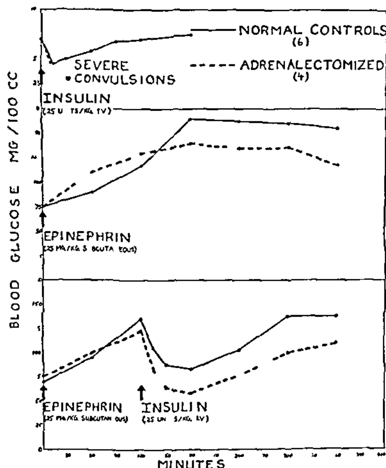


FIG 9 Effect of epinephrin and insulin on blood glucose level of normal dogs and adrenalectomized dogs maintained with pellet of d soxycort co terone acetate *After* Lewis R A Kuhlman D Delbue C Koepf G F and Thorn G W Endocrinology 1940 XXVII 9/9

glycogen into the three carbon compounds involved in the intermediary metabolism of sugar Consequently animals deficient in these secretions

fail to resist the effects of insulin phlorhizin or even of prolonged fasting Instead the materials from which glucose or glycogen reserves would be manufactured normally are combusted rapidly and even such reserves as exist soon are depleted This wasting of body stores involves not only carbohydrate but also protein stores It is possible furthermore that stores of fat may be concerned also but this is not known definitely at the present writing (1942) It is clear at least that the characteristic

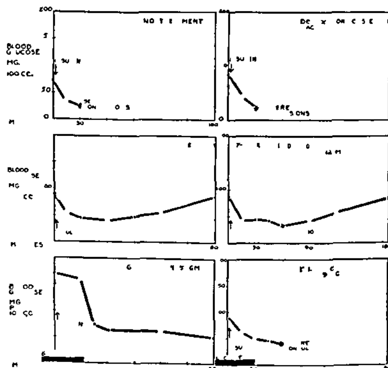


FIG 10 Effect of injected glucose and lactic acid and effect of adrenal cortical hormone therapy on blood glucose of adrenalectomized dog (211) following intravenous administration of insulin (0 25 U/kg) After Lewis R A Kuhlman D Delbue C Koepf G F and Thorn G W Endocrinology 1940 XXVII 980

metabolic stigmata of diabetes mellitus cannot occur in marked degree except through the continued operation of these adrenal hormones To this extent the carbohydrate disturbance in clinical Addison s disease may be interpreted as the antithesis of clinical diabetes mellitus Theoretically it should be possible to relieve clinical diabetes by partial adrenalectomy provided that ample supplies of salt and desoxycorticosterone acetate were available to counteract any incidental derangement of electrolyte balance

The Overproduction Theory of Diabetes

In major economic depressions it is commonly disputed whether the trouble is due (1) to overproduction of goods or (2) to underconsumption of goods Much the same dispute has been current among investigators of carbohydrate metabolism in the past generation Whereas *the underconsumption of glucose was the hypothesis accepted generally* fifteen years ago the element of overproduction has been gaining adherents rapidly as our understanding of endocrine balance has increased Probably the final interpretation of diabetes mellitus will include both elements The overproduction hypothesis is of especial interest however, because it offers a rational explanation of diabetic ketosis

Antiketogenic Effect of Carbohydrate in Diabetes Mellitus

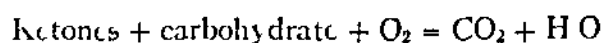
Because the fatal outcome of diabetic coma is brought about by the unusual metabolism of fat in that condition and because this fatality can be prevented through suitable regulation of the carbohydrate metabolism it is important to consider the interrelation of these two types of foodstuffs as regards ketosis Although in this section we shall consider chiefly carbohydrate when speaking of the so called antiketones it should be remembered that approximately half of the combusted protein behaves as if it were carbohydrate Stadie (1940) has described the *current and opposing hypotheses of fat metabolism in diabetes mellitus* as follows

1 '*Under utilization hypothesis* The major if not the sole defect in the intermediary metabolism in diabetes mellitus is that the peripheral tissue i e, chiefly muscle cannot either at all or in sufficient measure oxidize carbohydrate without the catalytic intervention of insulin

2 '*Overproduction hypothesis* Fatty acids are convertible into carbohydrates by the liver The function of insulin is to *control directly* or indirectly the extent of this conversion its action in the periphery which is to catalyze the oxidation of carbohydrate is either nil or of minor importance

It has been pointed out in the preceding pages that ketosis is the result of endocrine imbalance or at least that it depends upon the presence of certain hormones and that it can be thwarted by altering the existing endocrine status in the appropriate direction It was pointed out also that such a finding tended to cast doubt upon the hypothesis of Knoop (1904) that beta oxidation in the liver eventually yielded acetoacetic or betahydroxybutyric acids which cannot be destroyed further by

the diabetic individual According to this hypothesis the oxidation of ketone bodies was visualized qualitatively as follows



$$\text{Ketones} + \text{carbohydrate} + O_2 = CO_2 + H_2O$$

as Stadie (1940) has formulated the concept qualitatively

In recent years however much evidence has accumulated to show that ketone bodies are utilized for energy production by the muscles both of normal and of diabetic animals Part of this evidence has been reviewed by Stadie Zapp and Lukens (1940) who conclude not only that the diabetic animal can use ketones to furnish a large part of the basal energy requirement and of the requirement for work at a level four to six times the basal utilization but also that there was no significant relationship between the antiketones oxidized and the amount of ketone body burned

Accordingly Stadie has presented an alternative concept of fat metabolism in the diabetic which implies that far from being parallel the relation of fat metabolism to carbohydrate metabolism is an inverse one In Stadie's words Up to a certain level fat metabolism is complete and there is no ketonuria Beyond this level fat metabolism is incomplete and part of the fat catabolized is excreted in the form of ketone bodies

Indeed on the basis of clinical investigations in diabetic patients he was able to formulate an equation which expressed roughly the urinary ketone bodies as follows $E = (1 - k)\ (F - U_0)$ where F equals total fat catabolized in grams mM or equivalent mM of ketone bodies U_0 equals maximal aketonuric fat utilization E equals total urinary ketone bodies in mM of ketone bodies or the equivalent grams of mM of original fat and k equals coefficient of excess fat utilization Although this equation should not be taken too literally it does serve without too great distortion of facts to express the general trend of ketone excretion In general the maximal fat utilization possible without ketonuria seems to be about 34 ± 1 6 mM of ketone bodies per kilogram per day The coefficient of excess fat utilization may vary from 0 3 to 0 8 in different individuals

In using these equations the various terms must be expressed in the same units To this end the following equivalents are useful One gram of fat equals 1 15 mM of fat or 13 8 Mm of ketone bodies Likewise one mM of ketone bodies equals 0 0726 gram or 0 0836 mM of original fat

On the basis of such studies Stadie presents the following general concept of the total metabolism in an idealized diabetic patient who is

deriving one fifth of his caloric requirement from protein Such a pa tient at rest would escape ketonuria if the fat consumed were less than 2 5 grams per kilogram each day When total metabolism was low such a patient might escape ketonuria even though the carbohydrate burned were low Indeed the old Allen treatment of diabetes relied upon this feature

As caloric requirements increased however the proportion of con tributing carbohydrate would have to increase also in order to avoid ketonuria These general relationships for an idealized patient are rep resented schematically in Figure 11

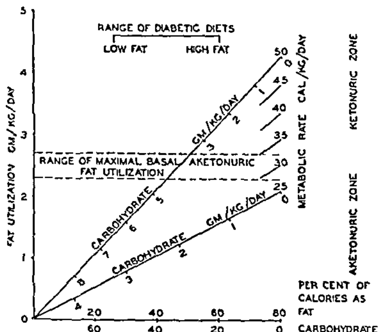


FIG 11 Schematic representation of carbohydrate and fat metabolism in diabetes mellitus and their relation to ketone body excretion After Stadie W C Jour Clin Investigation 1940 XIX 860

It should be emphasized that this figure which is based on metabolic observations made on patients studied in the clinic conforms to the hypothesis that the diabetic organism regularly utilizes ketone bodies in considerable quantity and utilizes them independently of carbohydrate oxidation It should be noted also that present-day empirical clinical experience has led to the use of such diets as would have been recom mended on the basis of the nomogram which is shown in Figure 11

CARBOHYDRATE REQUIREMENT

It was pointed out in Volume I Chapter V that a dog can live for long periods solely on meat which is very low in carbohydrate Even after starvation considerable stores of glycogen are found in the animal's body and this reserve fluctuates with exercise but can be removed entirely only by tetanic convulsions Indeed the liver glycogen is maintained at a rather high level on a purely meat diet Man however is unable to maintain health and body weight unless other food is supplied Although fat can compensate for lack of carbohydrate to a considerable extent there is a minimal quota below which carbohydrate may not be reduced without the occurrence of one or both of the following deleterious effects first body protein will be consumed as pointed out in Volume I Chapter V and second ketosis will result if the ratio of fat to carbohydrate being burned is too high

As regards this sparing effect of carbohydrate upon protein metabolism which was discussed at length in Chapter V of Volume I it will suffice here to point out that an ordinary diet in which half of the caloric value is contributed by carbohydrate and the rest by fat spares protein as well as one which is almost entirely carbohydrate In terms of actual amounts the results of Cathcart (1922) may be recalled He studied the effect of a diet consisting of about 300 grams of olive oil to which increasing amounts of glucose were added He attained minimal values for urinary nitrogen when 100 grams of glucose were added an amount representing about one eighth of the total caloric content Of course this minimal value probably would not be sufficient for a man doing strenuous work because under such circumstances there would be critical periods in which sufficient carbohydrate would not be available to protect body protein and transitory drain upon cellular protoplasm would result

In the last century with the development of horticulture and scientific methods of agriculture carbohydrate has tended to become increasingly prominent in human diets Because often nine tenths of the food value of grain is wasted if it is used to raise animals for meat it is obviously more economical to feed it directly to man Furthermore as already pointed out in this section sugar is the most readily available form of fuel for muscular activity and especially in time of physical stress the greatest sparer of body protein Within wide limits therefore this emphasis upon carbohydrate intake is harmless and indeed desirable The use of carbohydrate for example avoids the distension and diarrhea which usually follow the ingestion of too large quantities of fat On the other hand if too much starchy food be used fermentative diarrhea fre

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quently will result with certain clinical sequelae to be discussed in Part V Furthermore such a diet easily may be deficient not only in essential amino acids but also in minerals vitamins and similar accessory food substances

Antiketogenic Requirements

The other factor which limits the reduction of carbohydrate in the diet is the so-called fatty acid glucose ratio described in the pioneer work of Woodyatt (1921) Assuming that in the metabolism of protein *this foodstuff is converted into 58 per cent glucose* and 46 per cent fatty acid and assuming similarly that neutral fat yields 10 per cent. glycerin and 90 per cent fatty acid Woodyatt found that the organism must burn at least 1 gram of glucose like food in order to oxidize completely 1 5 grams of fatty acid This statement has received wide popularity in the summary statement that the $\frac{FA}{G}$ ratio should not exceed 1 5 if ketosis is to be avoided Many interesting papers have been written on this subject and are well summarized in the classic manual of Joslin and his associates (1940) Of course this value is at best an average one It is probable that persons like the Eskimos who are accustomed to diets high in fat may with impunity enjoy a $\frac{FA}{G}$ ratio of three or even higher Similarly Joslin found that if under carefully controlled circumstances the protein intake were reduced to as low as two-thirds of a gram per kilogram per day a somewhat higher ratio might be tolerated

Although there is no doubt of the observations summarized by the Woodyatt ratio there is now considerable doubt as to the interpretation which was held generally a decade ago Various authors at that time computed the number of molecules of antiketogenic substance needed to combust *perfectly a certain number of ketogenic molecules* Much work of this sort was performed by Shaffer (1922 1923) dealing both with metabolic studies and with chemical models in vitro Originally he concluded that the molecular ratio of antiketogenic to ketogenic material corresponds to the value 1 1 when computed in terms of glucose to fatty acid Indeed McCann Hannon Perlzweig and Tompkins (1923) studied the actual diets of diabetic patients on the verge of ketosis and verified Woodyatt s ratio of 1 5 which in fact corresponds to a molecular ratio of 1 1 Later however Shaffer doubled the ketogenic material which could be handled in his artificial models and Mason (1927) found that in four of five obese individuals undergoing reduction of body weight the ratio of

ketogenic to ketolytic molecules being burned lay between 1 5 and 2 0 without observable acidosis In other words these individuals required only half a glucose molecule to oxidize properly one molecule of fatty acid In summary then the significance of the Woodyatt ratio remains unexplained except as a statistical limiting equilibrium between two trends of metabolism of foodstuffs

Specific Dynamic Action

It will be recalled from Volume I Chapter V, that for every 100 calories of energy derived from protein some 30 will appear as increased heat production This specific dynamic action of protein is much more marked than in the case of sugars Nevertheless there seems to be little question that the feeding of various carbohydrates induces increased elimination of heat This problem was studied by Lusk (1915), who gave 50 grams of various carbohydrates to the same dog and observed the per centage increase of heat production over the basal metabolism The increased metabolism found during the second third and fourth hours was as follows for fructose 37 per cent for sucrose 34 for glucose 30 for galactose 22 for lactose 3 Using the Woodyatt pump to de liver glucose intravenously Boyd Hines and Leese (1925) were able temporarily to increase metabolism 48 per cent above the basal level An hour later however the increase was much smaller i e about 15 per cent Various postulates have been made to explain the increased metabolism For example acid intermediaries in carbohydrate metabo lism were supposed by F G Benedict to stimulate heat production in some unknown fashion Although the mechanism remains unknown the fact is that the respective increases due to amino acids to glucose and to fat seem to be additive when these three foodstuffs are administered together Moreover the relative effects for equal amounts of the three foodstuffs fall quantitatively in this order amino acid (e g , glycine) glucose fat

Carbohydrate Utilization in Exercise

In their revision of Bainbridge s classic The Physiology of Muscular Exercise Bock and Dill (1931) have pointed out that the energy expended by a marathon runner may call for the oxidation of about two pounds of carbohydrate or one pound of fat in less than three hours Under these conditions bodily reserve stores are drawn upon extensively In the more intense types of exercise such as the two hundred meter dash in twenty

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two seconds general body reserves can not be drawn upon and consequently the limiting factors are measured by such indices as the oxygen debt or the accumulation of lactic acid. These factors to be sure are themselves the resultants of many factors such as diffusion rates and circulation rate and in themselves can not be declared the cause of fatigue. They do indicate however that the carbohydrate cycle described in Part III has been stalled and that the chemical machinery within the muscle must be restored by rest.

Chemical Sources of Mechanical Energy in Muscular Activity – As pointed out in Volume I Chapter V some protein is destroyed (Kennaway 1908) and extra creatinin excreted (Leathes and Orr 1912) in severe exertion. These phenomena however ordinarily merely indicate structural wear and tear and can not be regarded as having great significance from the standpoint of energetics except in prolonged starvation or with a continuously inadequate caloric intake. The real fuel for muscular activity is derived from carbohydrate and fat either or both of them depending upon circumstances. The problem boils down therefore to the relative contribution made by each of these types of foodstuff under definite or peculiar conditions.

The final upshot of a mass of conflicting evidence seems to be that when both carbohydrate and fat are available the skeletal muscles use the former preferentially although fat is used also. The problem is complicated technically because most of the evidence rests upon determinations of the respiratory quotient which as explained in another section may not indicate the true energetics unless special precautions are taken to attain a steady physiological state.

Moreover low respiratory quotients are obtained during moderate work and high quotients in continuous heavy work as reported by Talbott Folling Henderson Dill Edwards and Berggren (1928). Indeed Dill Edwards and Talbott (1930) formulated this situation as follows: R Q = 0 04 (metabolic rate) + 0 817. This shift in the respiratory quotient may be interpreted as follows. When exercise is not too strenuous there is time to draw upon the fatty stores and convert them into small molecules which muscles can burn. When the pace becomes more strenuous however the preformed carbohydrate must be burned and the R Q accordingly is observed to rise. It seems likely that work up to four or five times the normal basal rate may be maintained with a resting quotient as indicated by the classical results from Katzenstein (1891) given in Table VII. When the metabolic rate has increased ninefold however the R Q may exceed a value of 0 9.

TABLE VII

	Oxygen Intake (c c /min)	Carbon Dioxide Output (c c /min)	R. Q
Rest	263.7	211.0	0.80
Walking on level ground	763.0	614.2	0.80
Climbing	125[illegible].2	1002.5	0.80

The interpretation of these values in terms of fuel consumed is that during rest or mild exertion about one third of the energy expended is derived from carbohydrate and two thirds from fat At higher rates of work such as forced marching the proportion of energy derived from carbohydrate increases to two thirds In mad sprinting carbohydrate alone is burned

These observations however must be modified further to cover the contingency that exercise is forced upon an organism whose stores of carbohydrate have already been depleted by starvation or by previous exertion Under such circumstances the proportion of fat used may be double Individuals vary considerably of course in their ability to support carbohydrate depletion One feature of this problem is that apparently about one seventh of the energy in fat is wasted in preparing it for consumption by muscles

Metabolism of Isolated Muscle — Despite many careful experiments (Evans 1912, 1914) it is still an open question whether the isolated heart uses fat in exertion Apparently it does use fat in fundamental basal metabolism Similarly Himwich and Rose (1929) have obtained evidence of the utilization of fat by dog s muscle exposed in situ In the isolated muscles of cold blooded animals however the evidence indicates an almost exclusive use of carbohydrate For example Winfield (1915) found that fat did not diminish in excised frog s muscle made to contract repeatedly A tentative answer might be that isolated muscles can burn fatty substances only after preliminary preparation usually by the liver In the absence of such fuel they consume either glucose delivered to them by way of the circulation or else their own glycogen

The utilization of this preformed muscle glycogen has been discussed in Part III It may occur in the absence of oxygen with the accumulation of lactic acid Subsequently much of the lactic acid is restored to glycogen at the expense of the combustion of other molecules of foodstuff e.g. lactic acid or glucose The observations of Hartree and Hill (1929)

indicated that the combustion of about one fifth of the lactic acid accumulated in muscle tissue sufficed to restore the remainder to its natural precursor state

Recovery after Exercise — A great deal of discussion is found in the literature over the question of the removal of lactic acid from fatigued muscles The two classical points of view have been stated by Meyerhof and by Lusk The former (Meyerhof Lohmann and Meier 1925) was that either lactic acid or carbohydrate may be combusted in order to restore the large accumulation of lactic acid after exercise The latter (Lusk 1928) claimed that the necessary energy might be supplied by the oxidation of fat especially when carbohydrate stores had been depleted In general it seems likely that as far as muscle tissue itself is concerned recovery from fatigue rests largely upon carbohydrate combustion Furthermore it seems most probable that circulating lactic acid is not a source from which muscle glycogen can be replenished although it is possible that some of the lactic acid remaining within the muscle may be converted back to glycogen Once a molecule of sarcolactic acid has escaped from the exercising muscle into the blood stream it probably has to go through the liver to be transformed into glycogen or glucose thence to be released as glucose before it can be taken up again by the muscle and stored as muscle glycogen In other words chemical recovery in muscular fatigue is not confined merely to muscles but involves the organism as a whole This conception often neglected in the clinic indicates why such diseases as cardiac failure pituitary failure or diabetes mellitus may prolong seriously the recovery after strenuous physical activity

Although the evidence for this point of view is too extensive to be cited in detail a few pertinent researches may be mentioned to indicate the type of information upon which this conception rests First of all it is well established that sarcolactic acid i e dextrorotatory lactic acid when fed or injected into animals is converted largely into liver glycogen (Cori and Cori 1929) Conversely after exercise in these animals the high initial liver glycogen continues to decrease for several hours during the ensuing rest period On the other hand the intra arterial injection of lactic acid into the hind limb of dogs does not produce any accumulation of glycogen in the muscles (Elias and Schubert 1918) Likewise in intact rats fasted for twenty four hours to reduce the store of liver glycogen Long and Grant (1930) found that after exercise the resynthesis of muscle glycogen was very slow On the contrary when glucose was fed after the exertion muscle glycogen rapidly increased whereas feeding sarcolactic acid aided the recovery but slightly It is apparent therefore that

the recharging of carbohydrate stores in skeletal muscle depends upon a supply of glucose either from food or from the liver and that the presence of insulin in the circulating blood or body fluids is a desirable adjunct

In connection with this need for insulin the experiments of Deboi (1930) are of especial interest He found that the recovery in the intact cat could be prevented by decapitation or even by simple bilateral section of the vagus nerves which control the secretion of insulin Removal of the pancreas likewise prevented the restoration of muscle glycogen stores a defect which could be remedied by the injection of insulin Such observations serve further to emphasize the statement made above namely that recovery from physical exertion is a complex process which involves diverse structures in the body and which is under endocrine control For example Long and Horsfall (1932) showed that infusion of glucose and insulin markedly facilitated the restoration to muscle glycogen of lactic acid injected simultaneously In fourteen control experiments the average muscle glycogen before lactic acid was injected into decapitated eviscerated cats was 0 61 per cent and after several hours of infusion of lactic acid it was still 0 62 per cent i e no appreciable change In striking contrast to these figures were those in similar experiments in which the lactic acid was accompanied by glucose or by glucose and insulin Thus the infusion of 5 per cent glucose with 5 per cent lactic acid raised the muscle glycogen from 0 67 to 0 72 and when a similar experiment was done with the addition of insulin the muscle glycogen rose from 0 70 to 0 99 Such well marked synthesis was not observed when glucose alone was infused The effect therefore was attributable to the lactic acid

Diets High and Low in Carbohydrate

In Volume I Chapter V a discussion was given of a few general principles governing the regulation of diets The problem in that chapter was the ability or necessity of being able to nourish adequately an individual on either a low or a high protein intake Much the same procedure may be resorted to in regulating the carbohydrate content of the diet Thus as shown in Table VIII it is necessary to provide a fundamental or elemental diet containing a sufficient quantity of the protective foods of McCollum and Simmonds (1929) Table VIII contains these foods with a minimum of carbohydrate The items, which are starred are essential and for them no substitutions may be made For those not starred however substitutions may be provided from the high carbohydrate foods in Table IX In this way it is possible to obtain a wide range of carbohydrate intake

TABLE VIII

ELEMENTAL DIET FOR ADULTS

Containing protective foods essential for normal nutrition

	Weight (gm.)	Measure (approximate)	Carbohydrate (gm.)	Calories
BREAKFAST				
10%[1] Fruit, citrus, or tomato, unsweetened	100	1/2 cup	10	40
Egg	50	1	0	70
Toast (or roll), whole grain	25	1/2 inch slice	12	65
Butter	15	1/2 oz. or 1 tablespoon	—	115
Coffee				
Light cream	30	1 oz.	1	60
LUNCH OR SUPPER				
American Cheese (or egg or small serving of meat)	30	1 oz.	—	110
3%[2] Vegetable or salad	100	1/2 cup cooked or 1 cup raw	3	15
Mayonnaise	15	1 tablespoon	—	100
Milk	240	1/2 pint	12	165
Bread (or roll), whole grain	25	1/2 inch slice	12	65
Butter	15	1/2 oz. or 1 tablespoon	—	115
10%[1] Fruit, unsweetened	100	1/2 cup	10	40
DINNER				
Meat, fish or poultry	100	3 1/2 oz. cooked, size of slice of bread	0	175
Potato	100	1 small	20	85
3%[2] Vegetable or salad	100	1/2 cup cooked or	3	15
6%[2] Vegetable or salad	100	1 cup raw	6	30
Butter or mayonnaise	30	1 oz. or 2 tablespoons	—	225
10%[1] Fruit, unsweetened	100	1/2 cup	10	40
Coffee or tea				
Light cream	30	1 oz.	1	60
Total			100	1590

These foods are essential. Additions and substitutions may be made from Tables IX and X. All measurements are level. 1 cup = 8 oz. [1] See Table XI. [2] See Table XII.

TABLE IX

HIGH CARBOHYDRATE FOODS

	Weight (gm)	Measure (approximate)	Carbohydrate (gm)	Protein (gm)	Fat (gm)	Calories
CEREALS AND STARCHES						
Bread	25	half inch slice	12	2	1	65
Muffins	40	1 medium	17	4	3	110
Roll	30	1 average	16	2	2	90
Griddle Cakes	50	1 4 inch diameter	14	2	[illegible]	80
Waffle	60	1 6 inch diameter	19	5	13	210
Cereals dry	30	1 cup	22	3	—	100
Cereal cooked	180	¾ cup	2[illegible]	3	—	100
Macaroni noodles Rice spaghetti	30	¾ cup cooked	2[illegible]	4	1	110
FRUITS AND VEGETABLES						
15% Fruits[1]	100	½ cup	15	—	—	60
20% Fruits[1]	100	1 small portion	20	—	—	80
Dried Fruits	30	¼ cup dry	21	1	—	90
20% Vegetables[2]	100	½ cup cooked	20	3	—	90
DESSERTS						
Cookies or	20	1 3 in diam	10	1	3	70
Crackers not sweet	6	1 2½ in sq	4	1	—	20
Cake plain	75	medium piece	35	3	10	40
Custard		½ cup or 4 oz	11	6	3	95
Doughnut plain	40	3 in diameter	20	3	8	160
Jello	65	3 oz	16	2	0	70
Ice Cream	100	¼ pint	20	4	13	15
Pie fruit		⅙ medium	66	3	16	420
Pudding		½ cup or 4 oz	40	6	[illegible]	250
SWEETS						
Sugar	5	1 teaspoon	5	0	0	0
Honey	20	1 tablespoon	16	—	0	65
Syrup	20	1 tablespoon	15	0	0	60
Jellies and Jams	0	1 tablespoon	15	—	—	60
Candy fudge	25	1 inch square	22	1	1	100

1 cup = 8 oz All measures are level

[1] See Table XI

[2] See Table XII

Because the diets mentioned may not be adequate in total calories it may be necessary to increase the fuel value of the elemental diet with additions from Table X which lists foods low in carbohydrate but high in fat Such foods of course yield maximal caloric intake per gram It

TABLE X

LOW CARBOHYDRATE FOODS HIGH IN FAT

	Weight (gm)	Measure (approximate)	Carbohydrate (gm)	Protein (gm)	Fat (gm)	Calories
Avocado	100	½ 4 inch fruit	[illegible]	[illegible]	18	190
Bacon	30	6 strips cooked	—	3	20	190
Butter	30	1 oz or 2 tablespoon	—	—	5	5
Cream light	30	1 oz	1	1	6	60
Cream heavy	30	1 oz	1	1	10	100
Fats and oils	15	1 tablespoon	0	0	15	135
French Dressing	1	1 tablespoon	—	—	9	80
Mayonnaise	15	1 tablespoon	—	—	1	110
Nuts	15	½ oz		3	9	100
Pork, salt	15	1 inch cube	0	1	12	110

All measures level

should be noted that whole grain bread is recommended in order to assure an adequate intake of thiamin Likewise when carbohydrate intake is low a considerable intake of protein is insisted upon because body protein is spared less readily if the carbohydrate consumption is minimal These protein containing foods likewise insure an adequate supply of iron and riboflavin In Table VIII the symbol 0 indicates no carbohydrate whereas a dash signifies a slight amount As shown in the table two servings of fruit should suffice to supply the essential constituents of the diet if three servings are impractical The lunch is planned for a left over dish or a sandwich For example it might consist of a salad or lettuce in a sandwich accompanied by milk and fruit Obviously a certain amount of imagination is needed to work out palatable and not too monotonous menus with this scheme in mind Table VIII calls for certain types of fruit listed as 10 per cent but obviously if one prefers 20 per cent carbohydrate fruit one prescribes half the serving of which Table XI gives a considerable variety Similarly the elemental diet recommends certain types of vegetables i e 3 per cent and 6 per cent carbohydrate vegetables as shown in Table XII Here again various substitutions are possible At best of course the scheme presented here is merely illustrative of the sort of readjustment which may be made if it is desirable to alter the diet The detailed carbohydrate contents and caloric values in the tables were arranged by Mrs Beula Marble

Sweetness is an important factor in diets and must be considered

TABLE XI

CARBOHYDRATE IN FRUITS

(grams per 100 gm.)

5%	10%	15%	20%
Rhubarb	Blackberries	Apples	Bananas
Strawberries	Cranberries	Apricots	Cherries, sweet
Watermelon	Gooseberries	Blueberries	Figs, fresh
	Grapefruit	Cherries, sour	Prunes, cooked (No added sugar)
	Lemons	Grapes	
	Limes	Loganberries	
	Melons	Nectarines	
	Oranges	Pineapple	
	Peaches	Pears	
	Tangerines	Raspberries	

TABLE XII

CARBOHYDRATE IN VEGETABLES

(grams per 100 gm.)

3%	6%	15%	20%
Artichokes, French	Beets	Artichokes, Jerusalem	Corn
Asparagus	Brussel Sprouts	Lima Bean, green	Beans — baked
Broccoli	Carrots	Peas	Beans — lima
Cabbage	Okra	Parsnips	Beans — shell
Cauliflower	Onions		Potatoes
Celery	Squash		
Cucumber	String Beans		
Eggplant	Turnip		
Endive			
Greens			
Kohlrabi			
Leeks			
Lettuce			
Mushrooms			
Peppers			
Radishes			
Sauerkraut			
Spinach			
Summer Squash			
Swiss Chard			
Tomatoes			

carefully if liquids are to be reinforced with simple sugars For this purpose lactose usually is preferred because it is inexpensive and not very sweet Fructose and glucose are more saccharine to taste although not so sweet as sucrose Sometimes the addition of a little salt will tend to counteract objectionable sweetness Similarly with concentrated sweets the addition of lemon or lime juice or of vinegar makes them more palatable

Easily Digested Carbohydrates

For invalids and convalescents it may be necessary to select the type of food carefully The following starchy foods when well cooked are easily digested Cereals toast crackers potatoes rice noodles macaroni spaghetti plain cake plain cookies simple puddings such as cornstarch and tapioca When fiber and roughage are contraindicated coarse cereals vegetables and fruits are strained Vegetables and fruits are cooked to soften their cellulose except that strained raw orange or grapefruit juice or tomato juice should be allowed daily The fruit juice often is tolerated better if diluted and if given following other food Very ripe banana may be used also without cooking Sugars jellies syrups and hard sugar candies usually are well tolerated when included with other foods In case of disturbed digestion such foods as beans cabbages radishes cucumbers melons blackberries and other seedy fruits are omitted from the diet

March 1 1942

PART V

CARBOHYDRATES IN DISEASE

In the clinical study of patients the chief use of quantitative clinical chemistry involving carbohydrates is in connection with the sugar concentration of blood and urine. These measurements commonly are used in the establishment of sugar tolerance curves employing glucose, galactose and sometimes fructose.

As has been pointed out in a preceding section of this chapter, the metabolism of these carbohydrates involves the function of the liver and the net balance among the various endocrine glands. In addition the state of the various storage depots for carbohydrate, i.e. the degree to which they are empty or replete, will determine in part the rate of disappearance of the sugar concerned from the blood stream.

Furthermore, if the carbohydrate be administered by mouth, its absorption by the alimentary tract, whether the alimentary tract be normal or diseased, will determine the rate at which the sugar appears in the blood stream. It is obvious that because of these and other complexities of carbohydrate metabolism the sugar tolerance curve is subject to numerous variations caused by other than disturbance in its utilization. For this reason its interpretation often may be conjectural or even frankly misleading.

Nevertheless, within certain limitations the sugar tolerance curve has been used extensively in the clinical study of several metabolic or endocrinological conditions. Such observations may consist of successive determinations of the blood sugar before and after the administration of sugar and the collateral measurement of urinary sugar. The carbohydrate may be administered either by mouth or intravenously and may be combined with a hormone like insulin or adrenin.

By appropriate combinations of this sort it is possible to put under strain certain mechanisms connected with the economy of carbohydrate and in this manner to test more vigorously the functional capacity of certain organs. The commonest uses of these curves are in suspected diabetes mellitus, in Addison's disease and hyperfunction of the adrenal cortex, in hypopituitarism, in acromegaly and in Cushing's syndrome. In addition the test has long been employed as a measure of liver function. In the following pages the application of sugar tolerance tests in these various conditions will be described and their interpretation commented on.

Sugar Tolerance Curves

Sugar Tolerance Curves in Diabetes

As stated in Part IV of this chapter in diabetes mellitus there exists not merely an excessive mobilization of energy stores in the body and particularly the conversion of such stores into carbohydrate but also a failure or diminished ability of the tissues to consume glucose. From this standpoint the increased blood sugar in diabetes is a beneficial compensatory phenomenon which facilitates the utilization of carbohydrate. In general under constant conditions of diet the height of the blood sugar during an interval of fasting determines the effectiveness of a standard dose of insulin in depressing the blood sugar (Scott and Dotti 1932). Indeed under standard conditions the fasting blood sugar levels both of normal and of diabetic patients are maintained within a definite range. The rise in blood sugar after the feeding of glucose is likewise constant and characteristic of a given individual under specific and reproducible circumstances. This point is illustrated by Himsworth's results shown in Table XIII. Thus the height of the blood sugar may be considered as a sort of "pressure head" which forces or enables the tissues to burn carbohydrate. Indeed Lusk (1928) explained the high respiratory quotient and increased oxygen consumption which follow the ingestion of glucose as due to the increased concentration of blood sugar.

The "pressure head" i.e. blood sugar concentration developed after the ingestion of a standard amount of sugar will depend as has been suggested upon the trend of carbohydrate metabolism within the tissues themselves and in particular on the sensitivity to insulin of the tissue cells. Himsworth (1935) has demonstrated that such dietary changes in glucose tolerance as are illustrated in Figure 12 can be explained by changes in tissue response to insulin. The data also suggest that in the normal individual the amount of insulin secreted by the pancreas is nearly constant but that the tissue responsiveness varies with circumstances. If the sensitivity of such an individual's tissues is decreased the tissues would tend not to use sugar advantageously but a compensatory increase in the height of the blood sugar level would result in normal sugar consumption. Conversely if the tissues should become unduly sensitive to insulin they would tend to use sugar unusually readily were there no compensatory fall in blood sugar concentration to bring about normal sugar consumption. As shown in Figure 12 after a prolonged diet low in carbohydrate the tissues are relatively insensitive to insulin. Indeed this effect simulates diabetes mellitus so closely that the question has been

TABLE XIII

CONSTANCY OF THE AREA DEMARCATED BY THE SUGAR TOLERANCE CURVE WHEN A DIET WITH CONSTANT AMOUNT OF CARBOHYDRATE IS BEING TAKEN

Subject	Diet			Area of glucose tolerance in mgm /min
	Carbohydrate	Protein	Fat	
I	100	80	218	6600 6500
II	50	80	240	9650 9450 8000
III	50	80	240	18 600 15 900
A	250	80	100	3500
	250	80	200	3527
	250	80	300	3534
B	55	88	202	11 960 13 690
	660	90	42	5590 5400
C	55	90	160	11 930 10 660
	660	90	42	4160 4550
D	56	87	255	10 890 11 100 10 750

The glucose tolerance areas were terminated at the shortest time taken by any glucose tolerance curve on the particular subject to return to normal The interval between different glucose tolerance tests on the same diet varied from three days to nine weeks The figures demonstrate that the greatest discrepancies between duplicate experiments are found when a low carbohydrate diet is being taken After Himsworth H P Lancet 1939 II 7

raised as to whether the high tolerance curve in diabetes is not to be regarded as a compensatory phenomenon

In general a prolonged restriction of carbohydrate in the diet impairs the sensitivity of the tissues to insulin and their ability to oxidize glucose and after prolonged starvation the organism may be unable to compensate

completely (Bauer 1929) Conversely continued high carbohydrate consumption tends to increase the insulin sensitivity of the tissues

Of course the difference between arterial and venous blood sugar is a rough measure of the amount of sugar consumed over a given period of time It is interesting therefore that as shown in Figure 12 the area between arterial and venous curves was the same in the two experiments given despite the fact that the blood sugar level was much higher in one case than in the other

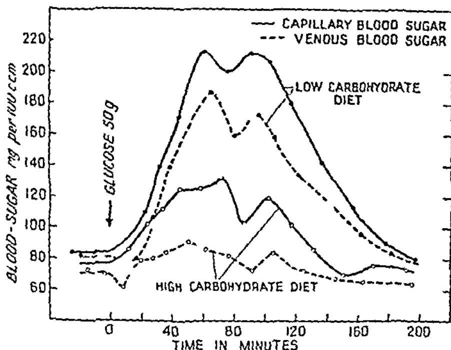


FIG 1 The tolerance of an individual for carbohydrate depends upon his previous dietary history On a low carbohydrate diet normal individuals lose their tolerance for sugar and exhibit an unusually high sugar tolerance curve After Himsworth H P Lancet 1939 II 5

Many factors combine in any given individual to influence the ability of the tissues to use carbohydrate Thus this capacity may be impaired by deficiency of insulin or by lack of oxygen Under such circumstances the carbohydrate head of pressure in the blood is adjusted through the behavior of the liver to the immediate needs of the tissues When the tissues need more sugar the liver secretes carbohydrate and thus increases the driving concentration in the blood To this end the liver in turn is

controlled by the anterior pituitary gland which when hyperactive accelerates the splitting of liver glycogen and the production of sugar from stores of protein and fat Thus the concept of homeostasis developed by Cannon (1929) has been extended to include as it were another dimension namely the need of the individual's tissues for a certain pressure head of glucose in the blood This ability is increased by insulin and decreased by secretion from the anterior pituitary as described in a

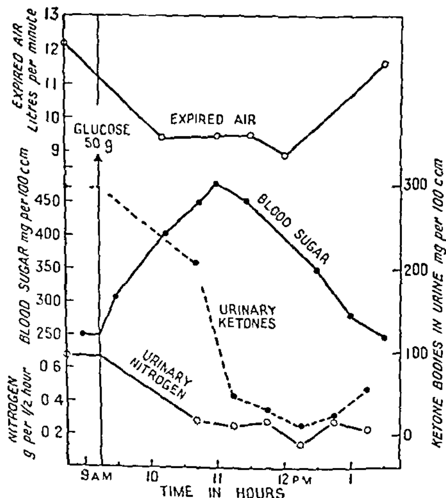


FIG 13 When a diabetic patient was fed glucose so that the blood sugar rose to high level the higher concentration of the glucose increased the rate of sugar combustion In other words the high blood sugar concentration was of advantage in favoring more efficient utilization of insulin Because of this increased combustion of sugar the urinary ketones and urinary nitrogen fell and concomitantly the acidosis abated After Himsworth H P Lancet 1939 II 1?

previous section In diabetes mellitus this same concept holds true as shown in Figure 13 When glucose was fed to such a patient the blood sugar mounted very high The resulting increased combustion of carbohydrate checked the ketosis and the breakdown of body protein It likewise concomitantly diminished the degree of acidosis as indicated by diminution in the hyperpnea

Two Types of Diabetes — When cases of diabetes mellitus are studied seriatim they fall conveniently into two general types i e the insulin sensitive and the insulin insensitive The first type presumably is due to a deficiency of insulin and occurs because adequate compensation cannot be made by increase in the blood sugar This type tends to be severe The second type seems to be due to insensitivity to insulin and under these circumstances compensation is more satisfactory Consequently such cases are mild as a rule This latter group can be imitated by the administration of extracts of the anterior pituitary Accordingly the question has been raised by Himsworth and Kerr (1939) as to whether pituitary hyperactivity may explain the pathogenesis of this type of the disease In such subjects who are on the verge of diabetes sepsis and obesity may precipitate diabetes by influencing untowardly their insulin sensitivity Paradoxically enough it has been suggested also by Himsworth that in this type a low carbohydrate diet may precipitate the disease contrary to established tradition that diets high in sugar should be avoided if one hopes to escape diabetes

In order to distinguish between these two types of individual Himsworth has devised the so called insulin glucose tolerance test This method measures the effectiveness of a standard dose of insulin in suppressing a rise in blood sugar due to the concomitant administration of glucose In practice a dose of insulin amounting to five international units per square meter of body surface is injected intravenously and immediately thereafter an amount of glucose approximating 30 grams per square meter of body surface is given by mouth As might be predicted from the nomenclature in both the normal and the insulin sensitive diabetic there tends to be a slight hypoglycemia and the eventual alimentary hyperglycemia is trifling In the insulin insensitive type however the blood sugar continues to rise much as it would were no insulin given In Figure 14 is illustrated a series of such tolerance curves in individuals of varying insulin insensitivity

As pointed out by Newbergh Conn Johnston and Conn (1938) the long recognized clinical distinction between the young thin severely ill diabetic and the elderly obese diabetic may be explained partially in terms of their respective abilities to oxidize glucose The members of the

elderly type ordinarily are insensitive to insulin, but due to the greater elevation of blood sugar they are able to consume nearly the same amount of glucose as normally Hence their disease is mild On the contrary in the young severely ill diabetic patient compensation is not achieved and due to poor oxidation of carbohydrate such cases tend to progress rapidly into severe ketosis and terminal coma Obviously the need for insulin in the treatment of this latter group is urgent but because of their sensitivity the danger of an overdosage of insulin is great In this latter type

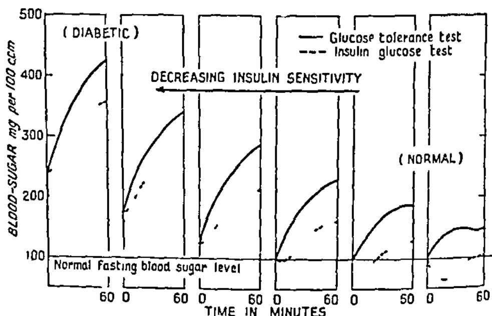


FIG 14 All intergrades of insensitivity to insulin may be found among individuals suffering from the insulin insensitive type of diabetes They may be distinguished by the glucose tolerance test and the insulin tolerance test At the left of the figure is represented a case of marked diabetes at the right of the figure is a normal control After Himsworth H P Lancet 1939 II 173

too there is the suggestion which requires further investigation that an excess of dietary sugar will have no great effect on the requisite dosage of insulin As one might expect in this group the administration of insulin greatly increases the difference between arterial and venous blood sugar concentrations demonstrated by Marble (1938) because the peripheral tissues are then able to burn large amounts of sugar Such is not the case, however in the insulin insensitive group

Himsworth has proposed a quantitative measure of the sensitivity to insulin of a given individual at a given time To this end he has suggested the use of the so called I/G ratio (Himsworth and Kerr 1939)

The meaning of the symbols is as follows G represents the area enclosed between the ordinary blood glucose tolerance curve and the fasting blood sugar level The symbol I represents the area between the latter curve and the insulin glucose curve i e the area change due to insulin In sensitive diabetics have shown an I/G ratio equal to $0\ 51 \pm 0\ 11$ indicating a small effect of insulin On the contrary in the sensitive diabetics the I/G ratio has been higher than 0 98 indicating a marked insulin effect It is striking that these groups of cases apparently are differentiated sharply one from the other according to the experience of Himsworth In other hands the differentiation has not been so clean cut Indeed some observers have doubted the existence of the two groups Probably the diabetic syndrome includes cases in which carbohydrate metabolism is interfered with at various stages Accordingly one is able to segregate groups of cases if one applies a sufficiently selective functional test

It should be emphasized that these distinctions are to be demonstrated clearly *only in the first hour of the tolerance test If the test is continued* for three hours the total effect of the insulin is approximately the same although the rate at which insulin has become effective differs in the two types This finding explains why the respective total insulin requirements per day tend not to show any marked difference when the two groups are considered in toto

There is some evidence that the members of the insulin insensitive group are the victims of pituitary hyperactivity Thus in the diabetes associated with Cushing s syndrome low sensitivity is found Low sensitivity likewise exists in dogs injected with anterior pituitary extracts In Young s permanently diabetic animals however marked sensitivity to insulin is found at the time when specimens of the pancreas show degeneration of the islets of Langerhans

In the detection of diabetes mellitus for diagnostic purposes particular stress should be laid upon the blood sugar level at two hours after administration of the glucose Thus Lozner and his associates (1941) have studied the tolerance of normal individuals and of patients to the intravenous administration of 25 grams of glucose The resultant curves were analyzed statistically and not until two hours after the injection of the glucose did the standard deviation from the mean become small enough to give significance to the glucose values These findings should stimulate a reconsideration of interpretations for diagnosis of glucose tolerance based on the shape of the curve or the area subtended by it during intervals shorter than two hours

At two hours an increase over the normal value of three times the

standard deviation was correlated in 95 per cent of the instances in which it occurred with the presence of clinical diabetes mellitus in the patient Other diseases associated by many authors with a decreased tolerance for glucose failed to show significant correlation, when the present criteria were used A study of hypoglycemia by the sugar tolerance method was shown not to be feasible since a large percentage of normal individuals exhibit this phenomenon around the 45 minute period

The intravenous use of 25 grams of glucose gave results at the two hour point which were independent of age sex height and weight of the subjects studied

For diagnostic purposes intravenous glucose probably affords the most accurate or reproducible test For therapeutic purposes however glucose often is more conveniently administered enterally by mouth by stomach or duodenal tube or by rectum There is no doubt that glucose solutions administered rectally are to a large extent absorbed, provided the concentration of glucose is not so high as to irritate the mucosa Thus Bergmark (1915) found that when a liter of 15 per cent glucose was administered by clysis about three quarters of the sugar could not be recovered Although there was no resulting hyperglycemia such clysis was in fact effective in relieving ketosis due to starvation

Sugar Tolerance Curves in Various Endocrinological Conditions

Inasmuch as the pituitary hormones according to C N H Long vary the porportions of carbohydrate protein and fat of the 'metabolic mixture they determine the extent to which these substances are conserved in body tissues For example the growth hormone conserves protein and the glycotropic hormone protects carbohydrate On the contrary the corticotropic hormone leads to the increased breakdown of protein into sugar (glyconeogenesis) through increased secretion of sterols by the adrenal cortex The total number of calories burned daily is determined largely by the thyroid hormone which may induce wide fluctuations in total metabolism without disturbing the constancy of the blood sugar provided the various other endocrines are balanced properly as described in the preceding section If the secretion of any given endocrine is weak it may be made manifest by a suitably arranged tolerance test

These concepts are brought out in Figures 15 and 16 taken from Fraser Albright and Smith (1941) In practice in order to test presumptive weakness or overbalance of certain endocrines these authors have used the following clinical procedures

1 *Glucose tolerance test* One hundred grams of glucose dissolved in one glass of water was used for all adult patients Blood samples were taken at 0 ½ 1 2 3 and sometimes 4 hours It has been decided to use in the future 0 8 gm of glucose per kg of ideal body weight as determined by a height age table

2 *Insulin tolerance test* One tenth of a unit of insulin per kg of wt was given intravenously It is now believed that a more scientifically

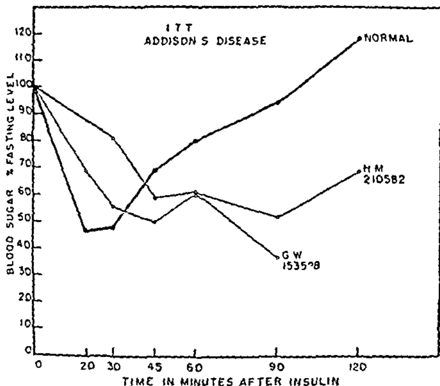


Fig 15 Insulin tolerance curves for two cases of Addison s disease as compared with the normal composite curve show (a) resistance to insulin and (b) lack of response to hypoglycemia After Fraser R Albright F and Smith P H Jour Clin Endocrinology 1941 I 300

correct dosage would be 0 1 U per kg of ideal weight as determined by a height age table Blood samples were taken at 0 20 30 45 60 90 and 120 minutes In most instances 0 01 c c of 1 1 000 adrenalin per kg of body wt was given intramuscularly after the 120-minute sample was taken Two more blood samples were then collected at 45 and 60 minutes thereafter Blood pressure determinations were made at the time the

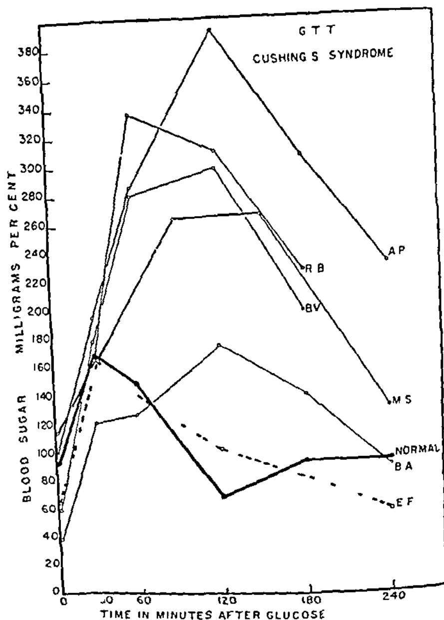


FIG 16 The glucose tolerance curves are shown for five patients with Cushin syndrome in contrast to that of a normal patient (heavy solid line) and that of a pati with adrenogenital syndrome (broken line) After Fraser R Albright F and Sm P H Jour Clin Endocrinology 1941 I 301

blood samples were taken and clinical symptoms of hypoglycemia were noted carefully both as to time of onset and severity These include faintness headache dizziness sensations of warmth perspiration palpitation tremor and sometimes visual disturbances In most cases these symptoms disappear about 15 minutes after onset but in cases of severe pan hypopituitarism Addison s disease or hyperinsulinism they are likely to persist for some time and the test may have to be terminated Clouding of consciousness is a grave sign and may be detected by the inability of the patient to answer questions intelligently or to carry on conversation in the usual manner The test may be interrupted by the administration of intravenous glucose or the patient may be urged to take dilute tea with a little sugar in it by mouth After the initial symptoms of hypoglycemia have worn off the patient often lapses into a state of lassitude and may sleep soundly it is always well to arouse him at the time of taking each sample and to note any clouding of consciousness After the test is concluded the patient is given a high carbohydrate meal and is told that he should have something high in carbohydrate content about 3 hours after the test is finished

Certain *precautions* must be observed In cases suspected of having pan hypopituitarism Addison s disease or hyperinsulinism one should start with ⅙ or ⅒ the calculated dose of insulin The symptomatology should be even more carefully noted

3 *Glucose insulin tolerance test* In this test the amount of glucose given is that given in the glucose tolerance test the amount of insulin that given in the insulin tolerance test Both the glucose and insulin are administered simultaneously and blood samples are collected at 0 20 30 45 60 90 and 120 minutes

Their experience with these tests may be summarized briefly as follows The *glucose* tolerance test elicits unresponsiveness to hyperglycemia either because of lack of insulin or resistance to insulin The combined *glucose insulin* tolerance test may be used to decide whether such unresponsiveness is due to hypoinsulinism or to resistance on the basis of hyperpituitarism or hyperadrenocortism The *insulin* tolerance test may help in some cases to differentiate pan hypopituitarism e g Simmonds cachexia from anorexia nervosa or primary hypothyroidism

A thorough experience with these procedures is essential to a proper interpretation of the results but certain of the clinical possibilities are illustrated in Figures 15 to 19 inclusive Obviously the endocrinological interpretation of these curves may be distorted badly if extraneous factors like gastrointestinal or hepatic disease complicate the picture

A fourth functional test which may be useful is the *adrenalin* tolerance

test with or without glucose In the study of Addison s disease Thorn and his collaborators (Lewis Kuhlman Delbue Koepf and Thorn 1940 Thorn Koepf Lewis and Olsen 1940) have made striking use of this procedure as illustrated in Figure 9

The application of such tests of course is only an indirect method of

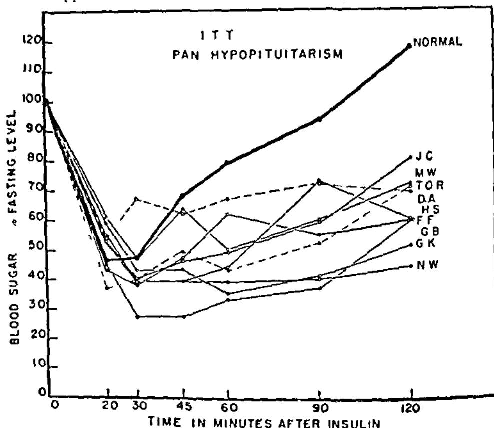


Fig 17 Insulin tolerance curves for nine patients with pan hypopituitarism compared with the normal composite curve After Fraser R Albright F and Smith I H Jour Clin Endocrinology 1941 I 303

testing the function of certain endocrine glands or groups of glands When specific methods ultimately become available for the direct measurement of each circulating hormone the use of blood glucose as an indicator of endocrine balance will be superseded by such more definitive tests

Glucose Tolerance Tests in Intestinal Disease

In Part III of this chapter it was noted that at any instant the level of blood sugar results from the combined effect of many processes

each proceeding at a different rate When glucose is injected the effect of intestinal action is almost completely eliminated but when the sugar is fed the rate of absorption becomes a major determinant in shaping the tolerance curve So constant is this effect in celiac disease for example that it is sought routinely as a confirmatory diagnostic finding (Fanconi 1928) A similar curve is found also in sprue (Thaysen and Norgaard

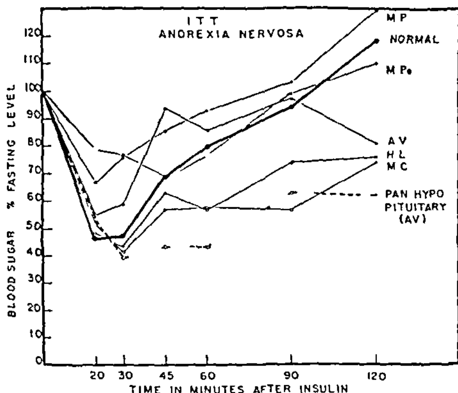


FIG 18 Insulin tolerance curves for four cases of primary hypothyroidism are compared with the normal composite curve and with the composite curve for panhypopituitarism (broken line) After Fraser P Albright F and Smith P H Jour Clin Endocrinology 1941 I 303

1929) in cretinism pancreatic disease infections and even in simple malnutrition (May and McCreary 1940)

It was believed formerly that in such conditions the explanation for the abnormally flat tolerance curve might be an abnormal renal threshold for glucose or a disturbance in the intermediary metabolism of carbohydrate The plain fact however as Ross (1936A) and others have shown is that in such diseases these metabolic factors tend to raise the general

height of the curve Even in normal individuals as shown in Figure 20 deprivation of carbohydrate affects the glucose tolerance Consequently in celiac disease the curve is flat despite general metabolic factors and the intestine itself seems to be the chief responsible organ

It is conceivable of course that diarrhea might be severe enough to whisk the ingested glucose through the alimentary canal so fast that

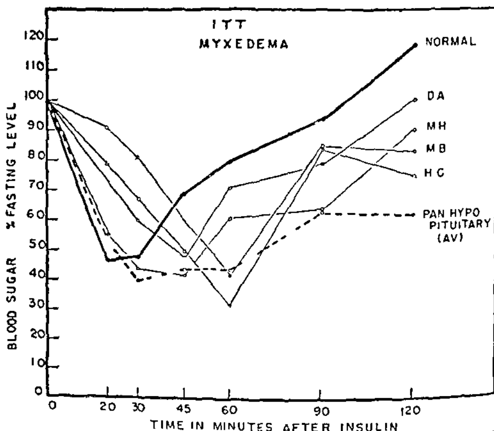


FIG 19 Insulin tolerance curves for five cases of anorexia nervosa are compared with the normal composite curve and with the composite curve for pan hypopituitarism (broken line) After Fraser R Albright F and Smith P H Jour Clin Endocrinology 1941 I 303

relatively little could be absorbed In animal experiments this situation is realized under certain conditions but in human enteritis this is usually not the case as shown by Ross (1936B) in abdominal tuberculosis The chief cause of the difficulty in short seems to reside in altered motility of the alimentary tract Such features as emptying of the stomach peristalsis and segmentation in the intestine according to May and McCreary (1940) are the important factors

Practically no glucose is absorbed by the stomach (Maddock Trimble and Carey 1933) and if this organ fails to empty normally the sugar can not reach the blood with normal speed In the small intestine two types of mechanical motility are important to efficient absorption i e the onrush peristalsis and the segmentation or champing contraction as described by Cannon (1911) If these movements are sluggish the sugar solution will pool in distended loops of intestine and thus the absorp

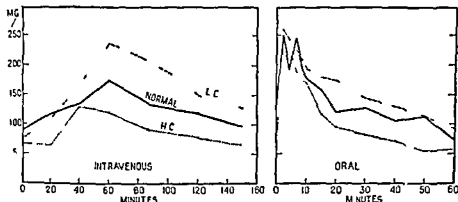


FIG 20 The two figures compare intravenous and oral glucose tolerance curves in a normal child The heavy line indicates the effect of a normal diet The broken line shows the effect of a low carbohydrate diet The dotted line shows the effect of reinforcing the normal diet with 150 grams of glucose daily After Ross C W Lancet 1936 II 557

tion will be impeded May and McCreary have studied this problem in children under the fluoroscope by means of barium sulfate administered with the glucose They found that in cases showing poor absorption clumping of the barium meal was observed in the roentgenograms When mecholyl was administered however the action of this parasympathomimetic drug induced vigorous segmental and peristaltic activity within three minutes Intestinal tonus returned and the lumen assumed normal size In every patient showing such a change a normal rise in the blood sugar was obtained In fact the artificially restored normal tolerance curve afforded an approximate preview of the ultimate curve obtained after convalescence in cases successfully treated This evidence suggests very strongly that in many intestinal diseases the flat sugar tolerance curve should be ascribed not to impaired function of the mucosa but to failure of normal motility of the bowel Of course such failure of motility can not be pathognomonic of any single disease entity however characteristic it may be

These observations have advanced notably our comprehension of the disease entity interpreted by Gee in 1888 as 'a kind of chronic indigestion' That other factors may be involved, however, is illustrated in Figure 21 which shows that the response to insulin may be altered due in part to poor absorption of carbohydrates In general however the net result of such factors thus far studied seems to be the opposite of the immediate effect due to absorption

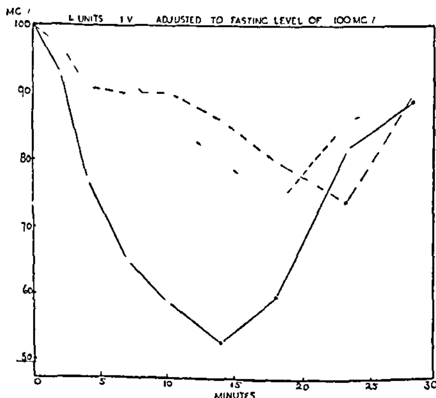


Fig 21 The depression in blood sugar produced by the intravenous injection of four units of insulin is illustrated by curves (1) for a normal patient on a normal diet (solid line) and on a low carbohydrate diet (long dashes) and (2) for a case of celiac disease (short dashes) The similarity of the effect of low carbohydrate diet to that of celiac disease is evident After Ross C W Trans Roy Soc Trop Med and Hyg 1936 XXX 41

In celiac disease as is well known there is also failure to absorb efficiently such materials as fat calcium and vitamins In other nutritional diseases however carbohydrate absorption may be normal Thus Helmer and Fouts (1937) found no consistent abnormality in the total absorption of ingested xylose in patients suffering from pernicious anemia

On the other hand it is possible to demonstrate diminished absorptive capacity of isolated segments of the diseased gut. Thus Groen (1938) studied several patients by the technique of Miller and Abbott (1934B) as described in an earlier section of this chapter. It should be noted that the result was judged in terms of a 50 cm length of intestine. Under these circumstances it was possible to discover a defective assimilation of

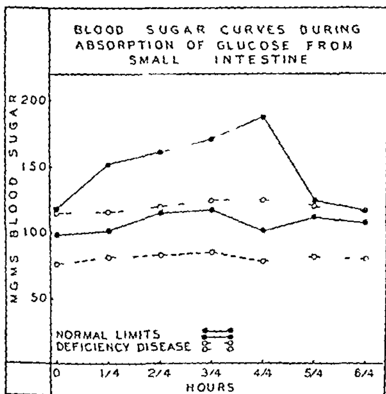


FIG 22 The upper and lower limits of blood sugar values following the introduction of x 100 c c of 15 per cent glucose solution into a 50-cm segment of small intestine are shown for normal individuals (solid circles) and in patients with defective absorption (open circles). After Groen J New England Jour Med 1938 CCXVIII 249

sugar as illustrated in Figure 22. Thus in diarrhea due to tuberculous enteritis, ulcerative colitis or nontropical sprue decreased absorption was demonstrated. Similarly in three cases of pernicious anemia and one case of alcoholic polyneuritis with pellagra diminished absorption was found before therapy and normal absorption after recovery. Six other cases of deficiency disease including two cases of scurvy however showed normal rates of absorption before treatment.

Such experiments suggest that the flat blood sugar tolerance curves often found in sprue and occasionally in pernicious anemia and certain other dietary deficiency states may be due partly to diminished absorptive capacity of the intestine Whether this defect is caused by prolonged lack of calories or of some derivative of the vitamin B complex is open to conjecture

Galactose Tolerance Tests

Galactose has been used extensively as a test of hepatic function because it is not utilized as such to any appreciable extent except in the liver where much if not all of it is transformed into glycogen Apparently this process is not influenced by the insulin supply available to the body tissues The test frequently has involved oral administration of the galactose followed by determination of urinary excretion This procedure gives variable results due to technical difficulties, which include variations in the rate of intestinal absorption and the absence of a renal threshold for this sugar Recently Bassett Althausen and Coltrin (1940) have suggested the use of an intravenous galactose clearance test to differentiate obstructive from parenchymatous jaundice In this procedure 1 c c of a 50 per cent solution of galactose per kilogram of body weight is injected intravenously within five minutes Seventy five minutes later the blood galactose concentration is determined At this time no galactose can be determined in the blood of normal subjects In patients with hepatitis or obstructive jaundice of less than six months duration there was a definite retention of galactose A great majority of the patients with hepatitis showed a concentration of over 20 mgm per cent whereas a large majority of patients with obstructive jaundice showed values below this level As with all functional tests the results must be repeated and integrated with the entire clinical picture

In thyroid disease Althausen and Wever (1937) demonstrated the tendency for a high blood galactose in hyperthyroidism after oral administration This result appears to be due to an increased rate of intestinal absorption Obviously this effect would seriously vitiate the result of the oral test as a measure of liver function in the presence of thyroid hyperactivity

Many papers have been written upon the value of the galactose tolerance test in the differential diagnosis of jaundice In uncomplicated obstructive jaundice the test usually is negative, whereas in primary hepatic lesions usually it is positive In chronic jaundice the results are of questionable value In the absence of jaundice the test rarely is of signifi

cance A good discussion may be found in a paper by Franklin White (1937) and one by Roe and Schwartzman (1933)

URINARY SUGAR

The normal urine probably contains well under 0 01 per cent of glucose (Shaffer and Hartman 1921B) although it contains variable amounts of reducing substances which may simulate as much as 1 5 grams of glucose in 24 hours When the blood sugar exceeds a certain concentration however even in the non diabetic subject the glucose concentration in the urine may exceed 1 per cent This blood level varies between 114 and 216 mgm per cent in arterial blood (Host 1925) When hyperglycemia subsides the kidney may continue to let glucose through even at a blood level below the normal fasting level Usually even after the ingestion of 100 grams of glucose the blood level fails to reach the concentration at which glycosuria begins In a small percentage of normal individuals however this concentration is exceeded and glycosuria may be demonstrable for several hours after the blood sugar level has fallen markedly There has been much discussion of this type of disturbance It was once thought to indicate latent diabetes mellitus but this interpretation now seems doubtful Furthermore Farber (1927) has described cases with a continuous or cyclic appearance of sugar in the urine which seem not to be related to classical diabetes mellitus In some persons with so called renal diabetes the kidney threshold is lower than the normal fasting blood sugar level and in consequence glucose is found constantly in the urine Such individuals never show ketosis and the amount of glucose excreted in the urine per day is independent of the carbohydrate content of the diet

Non Glucose Reducing Substances — A number of substances may appear in the urine of non-diabetic patients which give a so called false positive with Benedict s qualitative solution Thus concentrated urines from normal people may contain enough creatine to produce perceptible reduction In addition extraneous carbohydrate may occur as the result of slightly abnormal metabolism Usually it is possible to prove by appropriate fermentation tests that the offending substance is not glucose In general these unusual carbohydrates are not fermented by pedigreed yeasts as rapidly as is glucose Occasionally levulose and maltose are found Because levulose is fermented readily it must be identified by specific rotation or by special chemical tests After hydrolysis with mineral acid conjugated glycuronic acid may be set free and because this substance reduces Benedict s solution readily such urine might conceivably lead to confusion

Pentosuria is found not uncommonly It appears often in the urine of normal persons partaking of a diet rich in fruits berries or fruit juices In addition there is an essential pentosuria which occurs independently of the food This harmless anomaly is important only because it may lead to a mistaken suspicion of diabetes mellitus In certain cases the unusual carbohydrate is known to be xyloketose illus trated in Diagram X Likewise in alkaptonuria the homogentisic acid present will lead to a false reduction of the copper reagent Another very rare anomaly is galactosuria

Presumably due to retrograde secretion or diffusion from the breast lactose may occur in the blood stream and subsequently in the urine of pregnant or lactating women Nevertheless true hyperglycemia and glycosuria are found not infrequently in pregnant or lactating women and in recent years there has been a tendency to miss true diabetes mellitus on the assumption that the sugar was lactose Obviously in such cases a special investigation of the type of sugar or of the subject s blood sugar levels should be undertaken Incidentally a true glycosuria occurs at some time or other in about one in every seven pregnancies Most of such cases are benign but it must be remembered that diabetes often is noted for the first time during a pregnancy

Patients showing so called renal glycosuria should be observed for at least three years for possible progression of this condition to true dia betes At most the normal person excretes 1 gram per day of true glu cose in a concentration usually less than 0 04 per cent and amounts greater than this cast serious doubt upon the diagnosis of benign gly cosuria Incidentally Harding Selby and Armstrong (1932) have de scribed an afternoon glycosuria which may be benign but must be distinguished from incipient diabetes mellitus

Renal Clearance — In the study of kidney function and in particular of glomerular filtration certain carbohydrates have proved to be very useful as Smith (1937) has pointed out Such substances must be com pletely filterable through the glomerular membrane and must not be re absorbed excreted or synthesized by the tubules In a previous section of this chapter it was remarked that cane sugar when injected intra venously behaved like a foreign substance and was excreted largely in the urine Accordingly several other metabolically inert carbohydrates have been tested for the purpose It has turned out that xylose and inulin are especially suitable and as pointed out by Richards Westfall and Bott (1934) the advantage lies with the latter This starch like com bination of fructose molecules dissolves readily in hot water When cool the supersaturated solution may be injected intravenously Thereupon

it is excreted by the kidney quantitatively It appears in the renal filtrate within Bowman s capsule in the same concentration as in the plasma

By means of this substance it has been possible to gain important information regarding the function of the kidney in man and animals Thus in the average man it has been found that the glomeruli filter out about two ounces of water from the blood per minute under basal conditions It may be anticipated that the application of this method will yield important facts in the study of nephritis as well as of normal kidney function

Glycogen Disease

Von Gierke (1929) has described a syndrome which he named hepatonephromegalia glykogenica because the liver and kidneys were enlarged to several times the normal size and contained an excessive amount of glycogen There is also a cardiomegalic type in young infants in which very marked cardiac enlargement may occur and in which the individual muscle fibers are distended with glycogen (Humphreys and Kato 1934) Other organs may be involved e g skeletal muscle adrenals thymus spleen cartilage and central nervous system

The biochemical mechanism involved in this disturbance has not been deciphered although commonly entertained theories concern the liver amylase the anterior pituitary and the constitution of the polysaccharide Because Creveld (1939) has summarized the various clinical features of this recessive familial disturbance and it is described also in Volume IV Chapter VII–A of Oxford Medicine only a few biochemical aspects of the disturbance need be mentioned here As might be expected from Stadie s study of ketosis already described in Part IV of this chapter this carbohydrate disturbance is accompanied also by deranged fat metabolism The liver often is infiltrated markedly with fat and marked lipemia may occur (Hogg and Sidbury 1937) In addition Wilder (1935) has found that these patients fail to retain physiological saline solutions well

In consequence of the failure to mobilize glycogen certain chemical phenomena occur which might well be predicted from the general scheme of normal carbohydrate metabolism already presented Among these features as described by Ellis and Payne (1936) are the following a low fasting blood sugar e g 50 mgm per cent increased blood glycogen e g above 15 mgm per cent an abnormal oral glucose tolerance curve e g a delayed fall an unusual response to fructose e g an early rise in blood sugar in some cases frequent ketonuria especially in the morning and increased blood cholesterol

It will be observed that most of these difficulties can be understood if one assumes that the conversion of glycogen to blood sugar is impeded From this concept follow other incidental findings For example in association with high blood glycogen glycogen may appear in the urine (Naish and Gumpert 1936) As might also be anticipated Rauh and Zelson (1934) found marked sensitivity to insulin In glycogen disease nature has presented us with an admirable natural experiment in which to verify and pursue our present concepts of carbohydrate metabolism

Gaucher s Disease

In the first part of this chapter mention was made of the cerebroside kerasin which contains galactose Just as glycogen accumulates in various organs in von Gierke s syndrome so kerasin accumulates in Gaucher s disease Presumably in both of these diseases essential enzyme systems dealing with the respective carbohydrate derivatives are defective Because kerasin is also a lipoid derivative and has been described in relation to Gaucher s disease in detail in Volume IV Chapter VII–A, it need not be considered further in this section

Intestinal Carbohydrate Dyspepsia

It is rare to find that the ingestion of sugar produces acute disturbance of a serious nature In the glucose tolerance test it is common to administer 100 grams at once and in the convalescent treatment of hepatic necrosis nearly a pound of sugar may be consumed day after day for many weeks Of course a diet consisting solely of purified sweets may lead ultimately to deficiency disease and dental caries but these disturbances are the indirect rather than the direct consequences of the high sugar diet

When large amounts of starchy food are ingested however digestive disturbances may follow Minot (1941) has pointed out that this is particularly common in asthenic poorly developed individuals who take little exercise and complain of chronic fatigue When the disturbance is severe and continuous there may be lack of power of concentration irritability and emotional instability In such individuals the starch granules are not digested and absorbed efficiently in the small intestine The undigested carbohydrate passes into the colon where bacterial fermentation produces gas and so causes flatulence mild colic and diarrhea If this process continues for many weeks there is some suggestion that the absorption of accessory food substances may be interfered with

Such individuals suffer from migrainous or "bilious" attacks with loss of appetite, mild colic, furred tongue, anorexia, nausea and vomiting. In between attacks there is lassitude and abdominal distention due to colonic gas with borborygmus and marked flatus, especially at night. Aerophagia and belching are common symptoms.

When the fresh stool of such an individual is examined, it is found to be semiformed, sour smelling, acid to indicators like bromthymol blue, and riddled with a myriad of gas bubbles. Gross particles of undigested vegetable matter may be present, such as undigested beans, kernels of corn (maize) or pieces of potato or beet. Usually, tests for occult blood are negative if performed with the acid ether extract of the stool, but false positives with gum guaiac or with benzidine may be found if special precautions are not taken to exclude vegetable matter. Microscopic examination of the emulsified stool mixed with tincture of iodine reveals the presence of many starch granules. Roentgen study of the patient with the barium meal reveals rapid intestinal rate, especially in the small intestine.

The treatment of such individuals consists in the exclusion of starchy and cellulose foods of high residue. Beans, corn, squash, celery, turnips and cabbage leaves are particularly severe offenders. Even very fatty foods may add insult to this injury. The diet at first should contain very little residue, i.e., should consist chiefly of eggs, scraped beef, zwieback, jelly, cream, clear soup, orange juice, tea or coffee and sugar (sucrose). The patient should be kept at rest until he demonstrates that he can digest satisfactorily a diet containing an adequate caloric intake. Vitamins in concentrated form may be required. Later puréed vegetables, stewed fruits, roast meats, cheese, blanc mange and custards may be added cautiously and in small amounts. Unhurried meals and attention to careful mastication should be encouraged. Regular hours at toilet and strict abstinence from catharsis are desirable. The disturbance is likely to recur during periods of overwork and anxiety or of travel.

On the Toxicity of Glucose

Is moderate hyperglycemia harmful per se? This question has plagued many a medical student and clinician. Joslin and his associates (1940) have long pointed out that the blood sugar is a convenient index of metabolism and have advocated that the diabetic patient be maintained as nearly normal as possible. On the whole this viewpoint is sound advice. It does not, however, meet directly the academic question involved, namely, as to the toxicity of glucose. To avoid confusion it may be

mentioned that this question has nothing to do with the irritating effects of glucose solutions which are hypertonic Because isotonic glucose solution is approximately five per cent in concentration it is clear that more concentrated solutions may produce irritation or even inflammation The present problem however concerns possible undesirable metabolic effects

In the extreme glycosuria of the severe diabetic the concomitant polyuria undoubtedly contributes to dehydration Without marked polyuria however and in the absence of ketosis it is hard to show that hyperglycemia in itself produces harm Many of the older physicians and surgeons still believe that high concentrations of glucose e g 200 to 400 mgm per cent favor bacterial infection and prevent wound healing Recently however Greene Swanson and Jacobs (1940) deliberately have maintained hyperglycemia in surgical patients and reported that no deleterious effect could be demonstrated

Other considerations have been advanced in regard to this problem Does the constantly high blood sugar lead to excessive stimulation of pancreatic islet cells which might recover greater ultimate function if allowed to rest? Does the high blood sugar per se necessarily indicate perverted lipoid metabolism and thus augur impending arteriosclerosis? These are problems which future investigations must answer

In the meantime unfounded faith in the innocuousness of glucose must not be allowed to apologize for sloppy therapy in diabetes mellitus Nor must the convenience of the blood sugar determination as an index of normal metabolic balance blind us to the scientific possibility that this indicator in itself may be only a secondary variable in the progress of endocrine disease

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PART VI

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CHAPTER VI

THE REGULATION OF ACID-BASE EQUILIBRIUM

By John P. Peters

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Introduction

The term "acidosis" has been used at different times and by different authors to describe various conditions the overproduction of ketone bodies in carbohydrate starvation, the accumulation of other non volatile or volatile (CO_2) acids in the blood or depletion of the alkaline metals of the blood or tissues Not only has the same term been used for all these conditions but also too often the same therapy At first the confusion in both terminology and therapy arose largely from ignorance of the true distinctions between these various disturbances Gradually some insight into the nature of the disturbances and the underlying mechanisms by which they are produced has been gained But it has been gained chiefly by extension of acid base equilibrium studies to include more and more factors At the present time discussion of acid base equilibrium can not be confined to carbon dioxide bicarbonate, hydrogen ion concentration and ammonia production It must also cover the total water and salt exchange and the metabolism of organic substances The purpose of this chapter is to present the general theory of electrolyte and acid base equilibrium in health and disease pointing out the established facts and inferences that may be drawn from them with their bearing on clinical problems

The State and Distribution of Base in the Body

The basic elements of the blood and tissues must be composed almost entirely, if not entirely of the alkaline metals sodium potassium, calcium and magnesium The minute amounts of rarer alkaline metals, ammonia and organic bases which have been demonstrated, are quite negligible Of these four metals calcium and magnesium occur in relatively low concentration in body fluids and tissues other than bone and play a less important rôle in the maintenance of general electrolyte and acid base equilibrium than do potassium and sodium

At a reaction as nearly neutral as that which prevails in the body these alkaline metals can exist only in combination with acids as neutral salts and the sum of acid and basic equivalents must be practically identical These two relations are shown graphically in the first figure (Fig 1) and can be expressed in the form of an equation

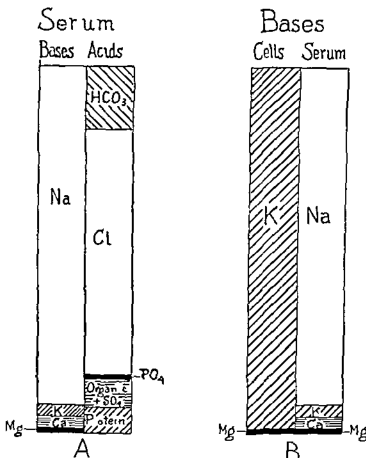


FIG 1 — A shows the relative concentrations of the bases and acid in normal blood serum B shows the relative distribution of base between the cells and serum of normal blood

$$[A] = [HCO_3] + [Cl] + [HPO_4] + [H_2PO_4] + [SO_4] + [\text{Protein}] + [\text{Organic acid}] = [Na] + [K] + [Ca] + [Mg] = [B]$$

where [A] and [B] represent the total concentrations of acid and basic equivalents, respectively the other symbols the concentrations of individual acid

I

THEORETICAL CONSIDERATIONS

INTRODUCTION

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of the total electrolyte content of any body fluid medium. The relative concentrations of the individual components vary from one medium of the body to another. Nevertheless such analytical data as are available indicate that the general principle expressed in the equation holds for all these media.

From direct measurements of the osmotic pressure of the serum and other body fluids and from theoretical considerations it is evident that the electrolytes (and this is synonymous with base) are the chief osmotically active components of the organism. Total base concentration must therefore be a major factor in the determination of the state of hydration and the fluid exchange within the body. It also must play an important part in determining the acid base equilibrium because it is the factor which limits acid combining power.

Variations in the Distribution of Base in the Organism

The distribution of base within the body varies from both a quantitative and a qualitative standpoint. This seems strangely at variance with the facts that osmotic equilibrium prevails throughout the body and that osmotic pressure varies with the concentration of base.

The Quantitative Inequality of Distribution

The quantitative inequality of distribution can be best elucidated by an example. In spite of the fact that blood serum is in osmotic equilibrium with the contents of the blood cells, the concentration of base in the cells is appreciably lower than that in the serum. The latter in turn contains more base than an equal amount of lymph or transudate. The striking difference between these various media lies in their protein content. The concentration of electrolytes varies inversely as the concentration of proteins, being lowest in blood cells where protein is highest and highest in lymph where protein is lowest. The explanation of the variation lies in the fact that the protein molecule is so large that its volume appreciably affects the water content of the medium in which it appears. The proteins of the serum, for example, make up some 7 per cent of the volume of serum, so that only 93 per cent of the total volume is water or solvent. In the cells, owing to the presence of hemoglobin, the concentration of water is still further reduced. It is not the amount of solute in a given volume of heterogeneous material that determines osmotic pressure but the amount of solute per unit of water in that volume. Therefore, to produce osmotic equilibrium the concentration of electrolytes in any two media should vary directly as the concentration of water in those media. That is,

$$\frac{[B]_1}{[B]_2} = \frac{[H_2O]_1}{[H_2O]_2} \text{ or } \frac{[B]_1}{[H_2O]_1} = \frac{[B]_2}{[H_2O]_2}$$

and basic equivalents, and the brackets indicate that these concentrations are expressed in terms of combining equivalents (milli equivalents) *

In the table below are given the average quantities of acid and basic ions found in normal serum [37]

Table 1 Concentration of bases and acid in normal human serum

Bases	mg per 100 cc	Milli equivalents	Acids		Milli equivalents
Sodium	3 9	143	Bicarbonate	58 vols per cent	26
Potassium	19 5	5	Chloride	369 mg per 100 cc	104
Calcium	10 0	5	Inorganic phosphorus	3 5 mg per 100 cc	2
Magnesium	2 4	2	Protein	6 4 per cent	11
			Organic acid and sulfate		12
Total		155	Total		155

If the sum of the base equivalents, which is designated [B] in the equations (on page 307) is equal to the sum of the acids it follows that the total sum of active electrolytic components in the system equals 2 [B] if as in blood, the ions are predominantly univalent and if it be assumed that there is complete electrolytic dissociation hence the total base [B] may be used as a measure

It must be recognized that this equality of concentration of acids and bases only becomes apparent when both are estimated in term of combining equivalents The values are here given as milli equivalents mM The factors by which the usual values are reduced to milli equivalents are

$$\frac{\text{vols per cent (HCO)}}{2\ 4} = \text{mM}\,[HCO_3]$$

$$\frac{\text{mg per cent (Cl)}}{5\ 85} = \text{mM}\,[Cl]$$

$$\frac{1\ 8\ \text{(mg per cent of inorganic P)}}{3\ 1} = \text{mM}\ ([HPO_4 - [H_2\,PO_4]) \text{ at pH} = 7\ 35$$

because at this pH 80 per cent of the inorganic phosphorus must be in the dibasic form and only 20 per cent as the acid salt

$$\frac{\text{mg per cent inorganic S}}{1\ 6} = \text{mM}\,[SO\ ]$$

$$0\ 68\ \text{(per cent of protein)}\ (\text{pH} - 4\ 8) = \text{mM}\,[\text{protein}]$$

This equation was derived by Van Slyke Wu and McLean Jour Biol Chem 1923 lvi 765 from experiments on horse blood and is not strictly applicable to human blood

Organic acid can not be directly determined or estimated

$$\frac{\text{mg per cent (K)}}{3\ 9} = \text{mM}\,[K] \qquad \frac{\text{mg per cent (Na)}}{2\ 3} = \text{mM}\,[Na]$$

$$\frac{\text{mg per cent (Ca)}}{2\ 0} = \text{mM}\,[Ca] \qquad \frac{\text{mg per cent (Mg)}}{1\ 2} = \text{mM}\,[Mg]$$

The equation $\frac{[B]_c}{[H_2O]_c} = \frac{[B]_s}{[H_2O]_s}$ holds strictly only when the hydrogen ion concentrations of the media are at the isoelectric points of their proteins At a more alkaline reaction than this (and reactions throughout the body are more alkaline) more base is found in the medium containing the greater amount of

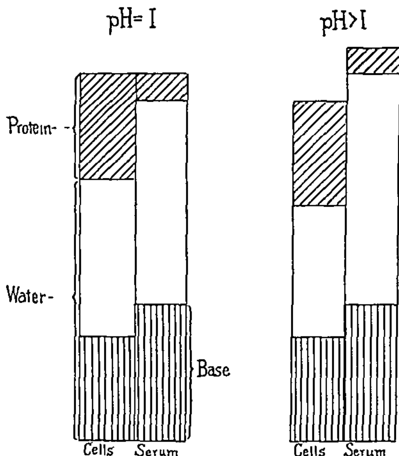


FIG 2 —pH = I shows the distribution of base and water between cells and serum at the isoelectric points of the blood proteins The proportion of base to water is the same in both media that is $\frac{[B]_s}{[H_2O]_s} = \frac{[B]_c}{[H_2O]_c}$ *The volume of water in the cell is ho ever smaller because th* protein concentration is greater Therefore the actual concentration of base per unit volume is less than that of serum

pH>I shows the changes that occur when the reaction becomes more alkaline than the isoelectric points of the blood proteins It may be seen that the serum imbibes water from the cells There is no transfer of base or protein but the shift of water causes the concentration of these two substances to increase in the cells and diminish in the serum.

where [B] has the same significance attached to it above, $[H_2O]$ represents the concentration of water, and the subscripts indicate different media The ratios of base to water in serum and cells are

$$\frac{[B]\ \text{serum}}{[H_2O]\ \text{serum}} = \frac{155}{93} = 167 = \frac{[B]\ \text{cells}}{[H_2O]\ \text{cells}} = \frac{112}{67} = 167$$

These are graphically represented in figure 2 (pH = I) The agreement between the two ratios is quite satisfactory Studies of Loeb, Atchley and Palmer[40] indicate that the differences between serum and transudates are determined by the same factors Differences in the total electrolyte concentration of tissues and body fluids in general, then, are mainly dependent on differences in the concentration of water in those media

The Qualitative Inequality of Distribution

If serum and blood cells are analyzed for specific alkaline metals, it is found that the base of serum is almost entirely composed of sodium while potassium predominates in the cells[37] (see Fig 1) This difference of composition between cellular and fluid phases is not peculiar to the blood, but seems to hold more or less throughout the body Sodium is the predominant base of body fluids potassium the chief alkaline metal of cellular contents The unequal distribution of these metals in the blood and the fact that changes in CO_2 tension cause water and acid ions to traverse the cell membrane without altering the distribution of base has led to the general statement that the blood cell membranes and probably other cellular membranes are impermeable to alkaline metal cations [9,57c]

Another important inference can be drawn and is supported by experimental work Potassium and sodium have diverse functions and are not interchangeable Blum[8] and others[38] have shown that the administration of sodium salts, especially alkaline sodium salts, produces or aggravates edemas of diabetes and some types of nephritis while potassium salts even alkaline potassium salts may act as diuretics in the same circumstances This may be an indication that such edemas involve only the interstitial fluids of the body and that the cells are not affected with the same hydrophilic tendency Gamble[0] has shown that measures which lead to the depletion of the water reserves of the body also cause sodium diuresis while potassium loss is an indication of cellular destruction

It has been stated that the base (or electrolyte) concentrations in two media in equilibrium with one another vary directly as the concentrations of water in those two media and that the intervening membranes (at least in the case of certain cells) are impervious to the alkaline cations sodium and potassium

of the body It has been shown already that the sum of the acids in the serum must equal the sum of the concentrations of the alkaline metals i e total base If for any reason any acid accumulates in excess in the blood either more base must be provided or some other acid must be displaced to restore equilibrium The former alternative would cause the osmotic pressure of the blood to rise and therefore would disturb other equilibria To prevent such a disturbance the body possesses mechanisms which permit the rapid excretion of acid with a minimal loss of water

The Respiratory Mechanism

The first and most responsive of these acts through the respiratory system About 15 to 20 per cent of the acid of the blood is carbonic a volatile acid continuously produced by the oxidation processes in the tissue cells which can be excreted by the lungs If any excess of non volatile acid accumulates in the body hyperpnea ensues and carbonic acid i pumped out of the blood liberating the base with which it was previously combined (as bicarbonate) to neutralize the foreign acid [7 44 57]

Intrinsic Defense

The body also has what might be called an intrinsic defense against acid It has already been shown that chloride passe into the cells in response to acidification in vitro The same thing may happen in life By this transfer of chloride ion the base which was previously combined with chloride i also rendered available for the neutralization of foreign acid Peters Bulger Eisenman and Lee [49 1] have shown for example that in diabetes accumulation of ketone acids may cause a reduction not only of bicarbonate but also of chloride in the serum

There is a quite as efficient intrinsic mechanism for defense against alkalosis If an individual ventilates excessively carbonic acid is pumped out of the blood and alkalosis (i e relative excess of basic cations over acid anions) would ensue if there were no compensatory reactions If the overventilation is sufficiently pro longed compensation may be established by substitution from the tissues of chlor ide ions which replace the depleted carbonic acid [43] The same reaction may compensate for the alkalosis produced by the hyperventilation of oxygen want [49] Even before chloride increases an excess of organic acids may appear in the blood chiefly ketone acids [17] at first later lactic acid This formation of organic acids Adlersberg [1] considers as one of the numerous reactions of the body against alkalosis It follows regularly not only the alkalosis of overventilation but also that caused by administration of bicarbonate and other alkalies [13 26]

protein This does not mean that base has traversed the membrane, but that water and acids have been transferred Disregarding for the moment, the chemical reactions involved, one may say that acid causes water, chloride and other acid ions to pass towards the medium containing the greater amount of protein alkali has the opposite effect In the case of the blood, for example, acidification by CO_2 or any other acid causes the cells to imbibe water and chloride from the plasma and therefore, to swell, alkali makes them shrink As base does not cross the cell membrane, its concentration must increase in the serum, when the blood is acidified and diminish in response to alkali This type of reaction is not confined to blood cells and serum, but occurs between any contiguous media in the body The reaction is graphically depicted in Figure 2, where pH = I represents conditions at the isoelectric point, pH > I at a more alkaline reaction

The Constancy of Base in the Body

Because it has such an important influence on phenomena of hydration and acid base equilibrium in the body the concentration of base in tissues and intracellular fluids is extremely constant [0] It is necessary at this point to draw a sharp distinction between concentration and content It is quite possible for the organism to retain or to lose indefinite amounts of base without altering the concentration of these substances in the body provided it retains or loses an equivalent amount of water Because this point has not been clearly recognized the most improper conclusions have been drawn from simple blood analysis through attempts to determine the presence or absence of electrolyte retention by the level of the electrolytes in the blood Because it is the concentration of electrolytes and not the content of electrolytes that determines osmotic equilibrium, there is a greater tendency to maintain constant concentration than constant content in the body And it may be added that disturbances of electrolyte concentration are far more disastrous than disturbances of content

Although Gamble [20] may have exaggerated the constancy of base concentration somewhat, he has demonstrated quite convincingly that measures, which reduce the water content of the organism lead to the excretion of an equivalent amount of base and conversely, measures which deplete base, are attended by an equivalent loss of water Increase of base entails retention of water, while accumulation of water is associated with storage of base

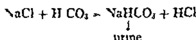
The Mechanism for Maintaining Constancy of Base Concentration

The mechanisms by which the constancy of base concentration is maintained are extremely complicated and delicately adjusted to meet the requirements

the body is able to convert a neutral substance urea into an alkaline salt and to substitute the alkali thus formed for a more essential basic metal An alkali of which an unlimited supply is produced in the course of normal metabolism, is sacrificed to spare one which can only be obtained from exogenous sources Recent evidence points strongly to the kidney itself as the site of the conversion of urea to ammonia[7, 37] The stimulus to ammonia production is not as has been generally taught increased hydrogen ion concentration of the blood The reaction instead seems to be delicately attuned as it is beautifully suited to the maintenance of the normal concentration of base in the blood[20] Ammonia excretion increases rapidly in all conditions which require the excretion of an excess of acid which could not otherwise be excreted at the reaction of urine without withdrawing an excess of base Strong mineral acid such as hydrochloric and sulfuric, can exist at the pH of urine only if they are completely neutralized Most organic acids found in urine must also be largely neutralized Therefore urinary ammonia increases when the demand for the excretion of such acids increases On the other hand it is not affected by acidosis due to carbonic acid against which the lungs provide an adequate defense[33] or by phosphoric acid acidosis which is taken care of by the transformation of phosphate described above[43] Van Slyke and his associates[37b] find that the ratio of ammonia titratable acid (both expressed as normal equivalents) in the urine of normal persons always exceed 0 8 and is usually greater than 1 0 This means that half or more of the acid in excess of the fixed base excreted daily in the urine is neutralized by ammonia

Urinary Bicarbonate Excretion

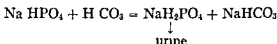
Against excessive alkali the body also possesses a renal defense If the concentration of base in the blood is increased absolutely or relatively meaning by the latter to cover those conditions like overventilation or vomiting in which there has been a reduction of the concentration of one or more acids without any change in level of the base itself the urine becomes more alkaline the urinary phosphate contains more of the dibasic or alkaline salt and ammonia excretion diminishes Furthermore bicarbonate appears in the urine[20] The excretion of bicarbonate in alkalosis is quite analogous to that of ammonia in acidosis An endogenous acid of which a limitless supply is afforded by the normal oxidative processes of the body is substituted for more essential acids of extraneous origin The reaction is illustrated by the equation



$$NaCl + H_2CO_3 \rightarrow \underset{\substack{\downarrow \\ \text{urine}}}{NaHCO_3} + HCl$$

The Function of the Kidneys in Maintaining Acid Base Equilibrium

These intrinsic mechanisms and the respiratory defense will not, of course, provide adequately against a prolonged excessive production of non volatile acids For such purposes a further mechanism is provided in the kidneys These organs are able to form an acid urine from an alkaline blood, a property which allows them to excrete acid in excess of base[33] The effect of this re action change is best illustrated by means of the phosphate excretion In the serum at the normal pH of 7 35, 80 per cent of the inorganic phosphate must exist as the dibasic salt, B_2HPO_4, in a highly acid urine more than 90 per cent may occur in the monobasic form BH_2PO_4 The reaction by which this change is effected may be represented by the following equation

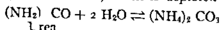


$$Na_2HPO_4 + H_2CO_3 = \underset{\text{urine}}{\underset{\downarrow}{NaH_2PO_4}} + NaHCO_3$$

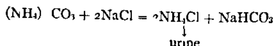
It is evident from the equation that this reaction saves the body an equiva lent of base for every molecule of phosphate thus transformed Urine phosphate increases in practically all conditions in which there is a demand for the ex cretion of an excess of acid without an equivalent amount of base If the organism were dependent for the urinary excretion of excessive acid upon the inorganic phosphate of the blood alone, this defense against acidosis would be quite inadequate, because the inorganic phosphate content of the blood is small Haldane[76] has shown that a certain proportion of the organic phos phorus compounds which are found in considerable abundance in the blood cells are rapidly converted to inorganic phosphate under the stimulus of acidosis and serve as a reserve supply to replenish the inorganic phosphate of the serum as the latter is excreted in the urine It is probable that the more extensive reserves in the bones can be drawn upon if the acidosis is suffi ciently prolonged, but before this happens the serum phosphate may fall ap preciably

Ammonia Production

More important than the phosphate transformation is the conversion of urea into ammonia and the substitution of the latter for a more essential alkaline cation By this reaction, which is depicted in the following equations,



$$\underset{\text{Urea}}{(NH_2)_2CO} + 2\,H_2O \rightleftharpoons (NH_4)_2\,CO_3$$



$$(NH_4)_2\,CO_3 + 2NaCl = \underset{\text{urine}}{\underset{\downarrow}{2NH_4Cl}} + NaHCO_3$$

ceptible of oxidation within the body such as lactates acetates citrates etc are quite similar in their action to bicarbonate because the acid radical is converted to carbon dioxide and water

Combinations of organic bases with mineral acid are seldom encountered They would undoubtedly tend to produce acidosis Ammonium salts of mineral acids e g ammonium chloride ammonium sulfate and acid ammonium phosphate $(NH_4)H_2PO_4$ are strongly acidifying because the ammonia is converted in the body into urea leaving the acid ion to be neutralized by base derived from other sources in the body especially bicarbonate and proteins [96, 8] The administration of ammonium chloride is therefore tantamount to the administration of an equivalent amount of hydrochloric acid

For a somewhat different reason mineral salts of the bivalent alkaline metals calcium magnesium and strontium are also acid producing [91, 96] The basic element of these salts is largely excreted in the stools as the insoluble salt of some other acid e g phosphate carbonate and fatty acid and the acid ion alone is absorbed The acidifying salts of this type most commonly employed are calcium chloride and magnesium sulfate

In the following table the various compounds which affect the acid base equilibrium have been classified according to their effects

Acidifying compounds

Mineral acid hydrochloric sulfuric phosphoric etc

Acid potassium and sodium salts of mineral acids monobasic potassium or sodium phosphates KH_2PO_4 or NaH_2PO_4

Ammonium salts of mineral acids ammonium chloride NH_4Cl ammonium sulfate $(NH_4)_2SO_4$ acid ammonium phosphate $(NH_4)H_2PO_4$

Soluble calcium and magnesium salts of mineral acids calcium chloride $CaCl_2$ and magnesium sulfate $MgSO_4$

Organic acids which are partly or totally unoxidized in the body uric benzoic hippuric etc

Neutral compounds

Neutral sodium and potassium salts of mineral acids the chlorides and sulfates of sodium and potassium

Ammonium carbonate

Ammonium salts of acids which are oxidized in the body

Organic acids which are completely oxidized in the body lactic citric acetic etc

Neutral sodium and potassium salts of organic acids which are not oxidized in the body urates benzoates hippurates etc

Alkalinizing compounds

Strong alkalies sodium and potassium hydroxide

Finally, if the alkalosis is severe or rapidly produced, ketone acids and lactic acid are excreted carrying with them into the urine extra base[13,76]

Bicarbonate excretion seems to be somewhat less perfectly adapted to the needs of the body than ammonia excretion It was pointed out that the latter responded not to all types of acidosis but only to those in which there was a specific need for conservation of base By analogy bicarbonate should be excreted in the urine only when there was an absolute excess of base (which as we shall see, is equivalent to an excess of bicarbonate) in the blood Nevertheless after overventilation, which increases the alkalinity of the blood while it diminishes bicarbonate urinary bicarbonate increases[13] This suggests that bicarbonate excretion is stimulated not by excess of blood base, but by diminution of the hydrogen ion concentration of the blood

Acid-Base Metabolism

Alkaline metals occur in the food as in the body almost entirely in the form of salts Although they may be combined with proteins and organic compounds the combination is that of an alkaline ion with an acid ion, easily dissociable They do not like sulfur and phosphorus, serve as structural units of complex substances such as proteins Because they occur as ions of simple salts they are readily transferred from one acid to another in the process of digestion and absorption Thus sodium proteinate may become sodium chloride in the stomach Calcium which appears as calcium chloride in the stomach, may become calcium stearate in the intestine Whether or not a given ion is absorbed will depend upon the solubility of the salt into which it is finally transformed It follows that sodium and potassium, which form highly soluble salts, are almost entirely absorbed from the alimentary tract and excreted in the urine while on the other hand calcium and magnesium which form insoluble phosphates, carbonates and salts of fatty acids are to a great extent excreted in the feces[53,76]

The effect of a salt on the acid base and osmotic equilibrium after absorption depends entirely on the ultimate fate of the individual ions of which it is composed Salts of strong mineral acids such as chlorides and sulfates, do not affect the acid base balance because they contribute equivalent amounts of acid and base which remain in the body or are excreted unchanged The effect of salts of weaker mineral acids is variable Dibasic sodium phosphate Na_2HPO_4 for example is weakly alkalinizing because o per cent of it must be changed to the monobasic form NaH_2PO_4 in the body Carbonates and bicarbonates act as alkalies because the carbonic acid which they contain is chiefly excreted by the lungs leaving most of the base to be eliminated in the urine in combination with other acids Salts of organic acids which are sus

line medium If then the contents of the intestine become more acid because of the acid nature of the diet or as the result of a systemic acidosis, a larger proportion of these alkaline metals is absorbed from the gut and finds its way into the urine where it serves to neutralize acid in this way sparing potassium and sodium

The Quantitative Constancy of the Base Concentration in the Body

It is obvious that any acid base exchange would be impossible if the base concentration of the body were absolutely constant Fluctuations do occur under physiological as well as pathologic conditions In health however these fluctuations are comparatively small and it is safe to say that the base concentration of blood and tissues is one of their most constant characteristics This constancy would be maintained with more difficulty were it not for the close relation between the exchange of water and that of electrolytes If for a time the supply of base exceeds its excretory powers the body by retaining water is enabled to keep the electrolyte concentration at the normal level Or if there is an excessive supply of acid and consequent depletion of base the excretion of extra water again restores the normal concentration The statement has been made and seems to hold in most instances that conditions which increase the concentration of acids in the blood invoke diuresis while conditions that raise the concentration of base result in water retention This is another way of saying that the total base and electrolyte content of the body is less constant than the concentration of the same elements

The Qualitative Constancy of the Base Concentration in the Body

It has already been pointed out that each one of the alkaline metals has a different distribution in the body corresponding probably to a special function The highly specialized actions of calcium and magnesium and the peculiar effect of the potassium ion on muscular and nervous irritability need not concern us here but the peculiar distribution of sodium and potassium must It must be obvious that though both have an equal theoretical value as base in neutralizing acid one can not be substituted for the other Retention and excretion of potassium will be controlled by the requirements and condition within the cells while sodium metabolism will be determined chiefly by factors which influence extracellular fluids Destruction of cellular tissue might increase the excretion of potassium without greatly affecting sodium extracellular accumulations of fluids would result in the retention mainly of sodium In states of healthy equilibrium the concentration of sodium and potassium must be individually quite as constant as the concentration of base as a whole

Alkaline salts of mineral acids dibasic potassium or sodium phosphate, K_2HPO_4 or Na_2HPO_4

Carbonates and bicarbonates of sodium and potassium

Sodium and potassium salts of organic acids which are oxidized in the body the lactates citrates, acetates, etc , of sodium and potassium

Acid Products of Metabolism

Besides the elements enumerated above certain other compounds, waste products of metabolism influence the acid base equilibrium These products are predominantly acid in nature Among them are some of the non oxidizable organic acids mentioned above The most important, however, are sulfur and phosphorus and especially the former These elements occur as parts of the intimate structure of certain proteins and other organic compounds sulfur especially in the amino acids cystine and cysteine, phosphorus in nucleoproteins and in phospholipoids such as lecithin Although a certain amount of both elements is excreted in the urine as neutral organic compounds part appears oxidized, as sulfuric and phosphoric acids The former is such a strong acid that even in an extremely acid urine it can exist only as a neutral salt Therefore, for every sulfate ion two equivalents of base must be excreted

It has already been pointed out that only negligible amounts of organic base are found in the body or its excreta The only alkaline product of metabolism of any importance is ammonia which does not aid in the neutralization of acid in the blood or tissues but is excreted in the urine in proportion to the requirements of the body to preserve the supply of alkaline metals essential for the maintenance of acid base and electrolyte equilibrium in the organism It may be considered then as a facultative product of metabolism only

It must be evident from the discussion thus far that the excretion of base is conditioned qualitatively and quantitatively not only by the amount of base and preformed and potential acid in the food but also by the quality and quantity of acid and base produced in the metabolism of the body and the state of hydration of tissue cells and fluids The mechanisms by which this excretion is effected have been detailed with one exception

The Function of the Bowel in the Maintenance of Acid Base Equilibrium

Calcium, magnesium and phosphoric acid all appear in considerable quantities in the stools in fact calcium and magnesium are mainly excreted by the intestines Shohl[53] has shown that the intestines play a not insignificant role in the maintenance of the acid base equilibrium of the body Calcium and magnesium are more readily absorbed from an acid than they are from an alka

Therefore $[\overset{+}{H}]^2 = K_w$ and $[H] = \sqrt{K_w}$ $[OH] = K_w$ and $[OH] = \sqrt{K_w}$
K_w has been ascertained to have a value of 10^{-14} at about 20° C which gives $[H]$ and $[\bar{O}H]$ of water values of 10^{-7}

In aqueous solutions it is impossible for the product of hydroxyl and hydrogen ions to exceed the dissociation constant of water In other words the equation $[H] \times [OH] = K_w = 10^{-14}$ holds for all aqueous solutions This makes it possible to express the value of $[OH]$ in terms of $[H]$

$$[\bar{O}H] = \frac{K_w}{[H]}$$

Equations similar to $\frac{[B] \times [OH]}{[BOH]} = K_{(BOH)}$ can therefore be changed to the form $\frac{[B] \times \frac{K_w}{[\overset{+}{H}]}}{[BOH]} = K_{(BOH)}$ That is the reaction of a solution can be expressed in terms of hydrogen ion concentration regardless of whether the solution is acid or alkaline It can be deduced that values of H less than 10^{-7} lie on the acid side, those greater than 10^{-7} on the alkaline side of the neutral point

Mathematical terms for Representation of Hydrogen Ion Concentration

Both K and [H] can be given simple arithmetical values Thus K_w can be written 10^{-14} or 0 00 000 000 000 001 and [H] or C_H as it is commonly written of neutral water is 10^{-7} or 0 00 000 01 This method of representation however is so cumbersome that logarithmic or exponential terms are more commonly employed

Sorensen introduced the use of the logarithm of the reciprocal of C_H because it gives comparatively small whole numbers He represents this value by the sign pH

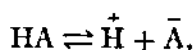
$$pH = \log \frac{1}{C_H} \quad \text{which may be written } pH = -\log C_H\ *$$

The dissociation constants can be and are expressed in the negative logarithmic form as pK pK = log 1/K In using the Sorensen logarithmic notation it must be borne in mind that pH varies inversely as C so that diminishing values of pH indicate increasing hydrogen ion concentrations

* To convert pH to C_H subtract pH from 0 – 10 to obtain log C Find the corresponding number from any standard table of logarithm For example if pH = 7 4 log C_H = 10 0 – 7 4 – 10 0 = 2 6 – 10 The antilog of 0 6 = 4 so $C_H = 4 \times 10^{-8}$ or $0\ 4 \times 10^{-7}$

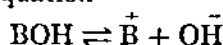
Hydrogen Ion Concentration

So far the total concentration of acids and bases alone has been considered without any attention to the reaction of the solutions in which they occur. The real degree of acidity of a solution is determined by the concentration of positively charged dissociated hydrogen ions which it contains, its alkalinity by the concentration of negatively charged dissociated hydroxyl ($\bar{OH}$) ions. When an acid or alkali or one of their salts goes into solution, it splits into a portion bearing a positive electrical charge, the cation, and a negatively charged portion the anion. In the case of acids the cation is hydrogen and it is this which gives them their characteristic properties. This reaction can be expressed by the equilibrium equation



$$HA \rightleftharpoons \overset{+}{H} + \bar{A},$$

where A = any acid radical. Alkalies derive their characteristic properties from the presence of an hydroxyl anion $\bar{OH}$. The dissociation of a typical alkali is indicated by the equilibrium equation



$$BOH \rightleftharpoons \overset{+}{B} + \bar{OH}$$

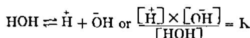
where B = any basic radical.

In the case of weak acids and bases, to which this discussion will be confined, the concentration of dissociated substance bears a constant relation to the concentration of the substance in solution. This means that the equilibrium equations above can be given quantitative form as mass law equations, becoming

$$\frac{[\overset{+}{H}] \times [\bar{A}]}{[HA]} = K \text{ and } \frac{[\overset{+}{B}] \times [\bar{OH}]}{[BOH]} = K$$

K, in each case, represents a constant that is peculiar to the particular chemical compound and is known as the dissociation constant.

Water dissociates both hydrogen and hydroxyl ions according to the equations



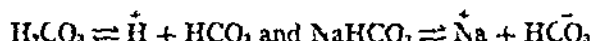
$$HOH \rightleftharpoons \overset{+}{H} + \bar{OH} \text{ or } \frac{[\overset{+}{H}] \times [\bar{OH}]}{[HOH]} = K$$

Because water is the solvent and hence of approximately constant concentration, the value of HOH in this equation may be considered constant and the equation may be written

$$[\overset{+}{H}] \times [\bar{OH}] = K_w$$

the values of the two constants K and $[H_2O]$ being combined into one, K. It is obvious that in pure water equal concentrations of hydrogen and hydroxyl ions must be dissociated, i.e. $[\overset{+}{H}] = [\bar{OH}]$.

In a simple mixture of carbonic acid, H_2CO_3 and bicarbonate, $NaHCO_3$ the following reactions must occur



$$H_2CO_3 \rightleftharpoons \overset{+}{H} + HCO_3 \text{ and } NaHCO_3 \rightleftharpoons \overset{+}{Na} + H\overset{-}{C}O_3$$

In spite of the fact that H_2CO_3 is not present in pure solution, the reaction of the mixture must be determined by the mass law equation

$$[H] = K\frac{[H_2CO_3]}{[HCO_3]}$$

However it is quite obvious that $[HCO_3]$ is formed from both the acid, H_2CO_3 and the salt $NaHCO_3$. In point of fact the acid is so slightly and the salt so completely dissociated that for practical purposes it can be assumed that all the acid present is in the undissociated form and that all the $[H\bar{C}O_3]$ is derived from the $NaHCO_3$.

The hydrogen ion concentration of the solution is therefore expressed by the equation

$$[H] = K_1\frac{[H_2CO_3]}{[NaHCO_3]}$$

in which K_1' includes the constant K of the previous equation and the dissociation constant of $NaHCO_3$. In negative logarithmic form this becomes

$$pH = pK_1' + \log\frac{[NaHCO_3]}{[H_2CO_3]}$$

In a solution containing bicarbonate and carbonic acid the reaction can be expressed by an equation of this form regardless what other substances may be present in the solution. These latter will only affect the value of pK_1. In serum $pK_1' = 6.14$ according to the latest studies of Van Slyke and his associates. pK_1' of whole blood and blood cells is somewhat higher.

In actual practice $[H_2CO_3]$ and $[NaHCO_3]$ are not directly determined. For $[H_2CO_3]$ the free CO_2 dissolved in the blood is substituted. This in turn is calculated from the equation dissolved $CO_2 = \alpha\, pCO_2$ in which α is the solubility coefficient of CO_2 and pCO_2 the carbon dioxide pressure in millimeters of mercury. $[NaHCO_3]$ is calculated as total CO_2 − dissolved CO_2. The equation, then becomes

$$pH = pK' + \log\frac{[\text{total } CO_2 - \alpha\, pCO_2]}{\alpha\, pCO_2}$$

Consequently the value of pK_1' depends in practice on the value given to α in this equation. Usually Bohr's solubility coefficient is employed. For serum at 38° C this is 0.712.

It is possible and simpler to express all mass law equations in logarithmic form Thus

$$\frac{[\overset{+}{H}] \times [\bar{A}]}{[HA]} = K_{(HA)} \text{ may be written } \log [H] = \log K_{(HA)} - \log \frac{[\bar{A}]}{[HA]}$$

or in Sorensen's notation

$$pH = pK + \log \frac{[\bar{A}]}{[HA]}$$

It should be clear from the discussion above that the strength of an acid or alkali depends on the value of its dissociation constant The weakest acids or alkalies are those which have dissociation constants nearest 10^{-7}

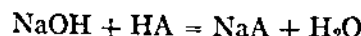
Buffers

Certain substances which are known as buffers by their presence in solution increase the amount of acid or alkali that must be added to cause unit change of hydrogen ion concentration or pH The most efficient buffers at reactions within the usual range of biological significance, are mixtures of weak acids or weak bases and their salts Their buffer effect is due to the relatively slight extent to which they undergo electrolytic dissociation, as compared with the almost completely dissociated strong acids and bases If a strong acid like hydrochloric for example, is added to a mixture of a weak acid HA and its alkali salt, BA the strong acid will react with the salt to produce the weaker acid according to the equation



$$HCl + BA = HA + BCl$$

The acid HA, instead of becoming completely dissociated like HCl, is only slightly dissociated Therefore the change in reaction is much smaller than it would have been had HCl been added to an unbuffered solution If a strong base, like sodium hydroxide be added to the same buffer solution it will be neutralized by the weak acid according to the equation



$$NaOH + HA = NaA + H_2O$$

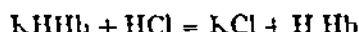
In a solution of a weak acid and its alkali salt Henderson[33] has shown that the reaction of the solution will depend on the ratio of salt to acid in the solution That is, the equation

$$[H] = K \frac{[\bar{A}]}{[HA]} \text{ becomes } [H] = K_1 \frac{[HA]}{[BA]}$$

$$\text{or } pH = pK + \log \frac{[BA]}{[HA]}$$

The explanation of this relation lies in the fact that the acid is almost entirely undissociated while salts of weak acids are almost completely dissociated

Their reactions to acid and base are quite comparable to those of bicarbonate If a stronger acid is added to a hemoglobin solution for instance the base combined with hemoglobin will neutralize the strong acid and the weaker hemoglobin acid will be formed instead



$$KHHb + HCl = KCl + H\,Hb$$

This should be more properly written



$$K_mH\,Hb + HCl = KCl + K_{(m-1)}H_{(\ +1)}Hb$$

Transfer of Ions and Water Across Cell Membranes

Blood plasma contains only a small amount of protein while blood cells contain large quantities of protein The cells therefore are highly buffered in comparison with the serum However by a fortunate provision the red blood cells are enabled to lend their buffer powers to the plasma by which they are surrounded The red blood cell membrane is apparently impermeable to both basic cations and to proteins but freely pervious to acid anions and the hydrogen ion[29 5] If an excess of acid for example carbon dioxide is added to the plasma of blood a certain amount traverses the cell membrane and penetrates the cells This reacts with the potassium hemoglobinate in the cells to form acid hemoglobin and potassium bicarbonate In this reaction potassium bicarbonate which is highly dissociated replaces the slightly dissociated hemoglobin salt In consequence the osmotic pressure within the cells rises To equalize this water passes from the serum to the cells and the latter swell[57]

Donnan[16] has shown that if two solutions are separated by a membrane which is impermeable to one or more ions contained in those solutions the ions to which the membrane is permeable will be distributed in the two media in a regular manner which can be expressed by an equation of the following form for univalent ions

$$\frac{A}{A'} = \frac{A}{A} - \frac{B}{B_i} = \frac{B}{B}$$

where A and A′ represent any two univalent anions and B and B two univalent cations while the subscripts denote the two media According to the Donnan equilibrium one would expect chloride and bicarbonate ions to be distributed in equal proportions between cells and serum That i

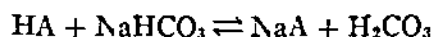
$$\frac{[\bar{Cl}]_c}{[\bar{Cl}]} = \frac{[H\bar{C}O_3]}{[H\bar{C}O_3]}$$

should hold If then the distribution of $[H\bar{C}O_3]$ changes that of [Cl] mu t

The Regulation of pH by Carbonic Acid and Bicarbonate

It follows from the equation that the reaction of blood and body fluids will depend on the proportions of carbonic acid and bicarbonate present It is important, then to consider the determinants of these two factors Carbonic acid is produced by the olution of carbon dioxide in water $CO_2 + H_2O \rightleftharpoons H_2CO_3$ Bicarbonate is formed by the reaction of alkali with carbonic acid $NaOH + H_2CO_3 = NaHCO_3 + H_2O$ Therefore, the relative amounts of bicarbonate and carbonic acid in solution and the pH will depend on the relative amounts of alkali available for combination with carbonic acid and the amount of carbon dioxide in solution Anything that increases the metabolism of course increases the production of carbon dioxide Anything which increases the respiration diminishes the carbon dioxide by pumping it out of the blood Ordinarily the respiratory mechanism responds so rapidly and accurately to the requirements of the body that the ratio of H_2CO_3 to $NaHCO_3$ and therefore pH remain practically constant [744] It is however doubtful whether blood pH is the specific respiratory stimulus as was formerly believed [134]

If a stronger acid than carbonic is added to the bicarbonate carbonic acid mixture it immediately reacts with the bicarbonate to form a neutral salt and carbonic acid by the reaction



$$HA + NaHCO_3 \rightleftharpoons NaA + H_2CO_3$$

In spite of the buffer action of bicarbonate this tends to increase the acidity of the solution If, however, sufficient CO_2 is removed, in the case of blood by the lungs the pH may be restored to its original level

The bicarbonate carbonic acid mixture then acts as an efficient buffer But besides this the fact that carbonic acid is volatile gives it a peculiar advantage over other acids in the maintenance of neutrality in the body

Other Buffers

Bicarbonate is not, however the chief or only buffer in the blood and tissues The most important of the other buffers are the salts of orthophosphoric acid, B_2HPO_4 and BH_2PO_4 and the proteins The value of phosphates in the renal regulation of acid base equilibrium has already been discussed The concentration of these salts in blood is so slight that they probably play a minimum rôle in the regulation of reaction There are however large quantities of organic phosphoric acid compounds in the blood cells which must have a considerable buffer value

The most important buffers in the body are the proteins and chief of these in the blood is hemoglobin At reactions prevailing in the body, proteins probably act as weak polyvalent acids combining with base to form salts

of hemoglobin also diminishes the fluctuations of blood pH which the rapid alterations of CO_2 tension would otherwise produce

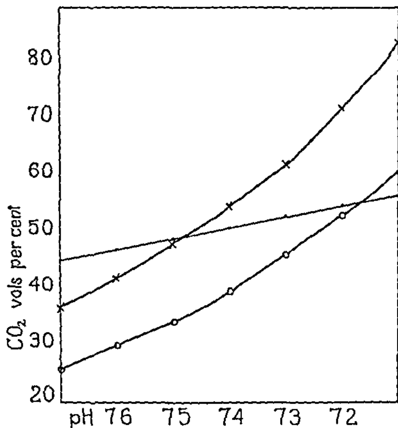


Fig 3 — The relative changes of CO_2 content and pH of whole blood o——o true plasma x——x and separated plasma —— produced by varying CO tension. This represents the change of pH caused by the addition of a given amount of carbonic acid True plasma is plasma which has been permitted to lose or gain CO_2 only when it was in contact with the blood cell Separated plasma is plasma which has been removed from contact with the cells and then exposed to different CO tensions

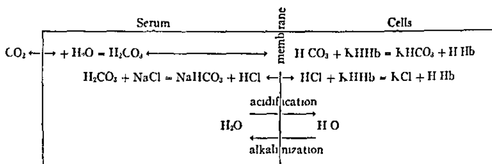
It is evident that the buffer power of plasma in contact with cells that is true plasma is much greater than that of separated plasma Therefore plasma in the blood must acquire buffers from the cells

II

Physiological and Pathologic Disturbances of Acid-Base Equilibrium

It must be evident from the preceding discussion that by the estimation of carbon dioxide or hydrogen ion concentration alone it is impossible to determine

change correspondingly * It follows that, when blood is acidified, chloride as well as bicarbonate and water passes into the cells from the plasma The sodium, with which the chloride was combined in the plasma, is liberated to aid in the neutralization of other acids, while the chloride which passes into the cells is neutralized by potassium derived from hemoglobin The chief reactions can be indicated roughly in the following manner



It has already been pointed out previously that, although the cell membrane is impervious to alkaline cations, the concentration of base in the two media is changed by the transfer of water (See also Fig 2) The contribution of the cells to the buffers of the plasma is illustrated in Figure 3 Similar shifts of ions probably occur between tissue cells and interstitial fluids and are important factors in the stabilization of reaction throughout the body

The Effect of Oxygen on Hemoglobin

One specific characteristic of hemoglobin must be mentioned before the discussion of the chemical aspects of neutrality regulation can be considered complete Barcroft and his associates [4] early showed that carbon dioxide and other acids accelerated the discharge of oxygen from the blood Christiansen Douglas and Haldane,[11] Parsons [47] and others [33b, 67c] have shown that oxygen in turn tends to drive CO_2 from the blood The mutual interaction facilitates the respiratory exchange of gases in both lungs and tissues In the lungs, as the hemoglobin becomes oxygenated it acts as a weak acid increasing the discharge of CO_2 On the other hand as the CO_2 tension of the blood falls its ability to absorb oxygen increases The effects are reversed in the tissues where absorption of CO_2 and delivery of oxygen are desired The change in reaction

* In actual point of fact $\frac{[Cl]_c}{[Cl]} = \frac{[HCO_3]_c}{[HCO_3]}$ does not hold for human blood if actual concentrations of these substances are compared Van Slyke Hastings Murray and Sendroy [67d] believe the observed inequality is due to different activity coefficients of the two ions In any case changes of distribution between the two media seem to follow closely the Donnan law predictions

larger amount of base and bicarbonate and alkaline instead of acid phosphate 4) Suppression of urinary ammonia excretion Primary carbon dioxide deficiency can be produced rapidly and easily by voluntary overventilation It may be observed in psychoneurotic patients and was not infrequently observed in the condition known as shell shock during the late war It is perhaps most often encountered in the post encephalitic syndrome [49] Whether or not tetany will develop seems to depend largely on the extent of the pH change which in turn depends on the speed with which the carbon dioxide is reduced and on the condition of the compensatory mechanisms If the chloride content of the blood has been reduced by vomiting so that the chloride response is impaired even moderate overventilation may cause tetany

The bicarbonate reduction which results from breathing air poor in oxygen is probably a primary carbon dioxide deficiency due to oxygen want Dyspnea and the compensatory reactions are not unlike those detailed above [45b] There is perhaps more tendency to lactic acid production as a specific result of the impairment of oxidative processes [35]

Prolonged immersion in a hot bath causes overventilation and carbon dioxide deficiency of a presumably similar nature [6] Whether all increases of body temperature are attended by similar changes has not been ascertained Increase of temperature diminishes the carbon dioxide carrying power of the blood increases the carbon dioxide tension and lowers pH in vitro [54]

Primary Carbon Dioxide Excess

Primary carbon dioxide excess is only encountered in ordinary life when the respiratory exchange of air is too small to remove from the blood the carbon dioxide formed in the processes of metabolism It can be produced experimentally by obstructing the respiratory passages or by breathing an atmosphere containing a high concentration of carbon dioxide The primary result is a diminution of the $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio and the pH of the blood [13] The compensatory response is transfer of Cl from the blood to the tissues to release base to combine with the excess of carbonic acid [30f] This increases $[NaHCO_3]$ and restores the normal ratio and pH At the same time it permits the maintenance of a higher carbon dioxide tension at a normal pH thus increasing the discharge of CO from the blood in a given volume of air Urinary ammonia excretion is not influenced because there is no tendency to excessive loss of base [37]

In emphysema and bronchitis the picture of primary carbon dioxide excess is regularly met [51] Plasma bicarbonate is high and chloride proportionately reduced [17 45f] A similar picture is sometimes encountered in cardiac decompensation especially if there is much pulmonary involvement [45f] However in the

the nature of a change in the acid base equilibrium It must be quite as evident that reduction of pH or blood carbon dioxide are not in themselves indications for the administration of alkali The remainder of the chapter will be devoted to a discussion of the various disturbances of acid base equilibrium, that may be encountered in health and disease, from the standpoint of both etiology and therapeutic implications

The types of acid base equilibrium disturbances can be classified in a general way according to certain criteria but it must be appreciated clearly that in actual practice almost any combination of disturbances may be met and that proper interpretation of chemical findings is only possible in the light of the fullest physiological and pathologic knowledge The following classification is offered and will be used in the subsequent discussion

- Primary carbon dioxide deficiency
- Primary carbon dioxide excess
- Excess of acids other than carbonic
  - Mineral acid acidosis
  - Organic acid acidosis
- Excess of base
- Deficiency of acids other than carbonic
- Deficiency of base (total electrolyte deficiency)

In any one of these conditions the pH of the blood may or may not be altered depending on the relative efficiency of the compensatory mechanisms, and especially the respiratory response[57a]

Primary Carbon Dioxide Deficiency

This term is used to distinguish reduction of bicarbonate as a result of over ventilation from the reduction that follows the accession to the blood of some other acid Primary carbon dioxide deficiency results only from excessive breathing The first effect of such overventilation whether it is produced voluntarily or involuntarily is to pump carbon dioxide out of the blood and tissues thus increasing the $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio and the pH If the reaction of the blood is sufficiently altered tetany may ensue[13, 43, 451] However, if the reduction of CO_2 is not too rapidly induced compensatory reactions may prevent the pH from changing[451] These compensatory reactions are 1) Increased production of the organic acids ketone acids and lactic acid, the latter may be the result of increased muscular activity associated with the development of tetanic spasms 2) Transfer of chloride to the blood from the tissues These acid combine with base formerly bound by bicarbonate thus liberating carbonic acid to restore the normal $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio 3) Excretion of alkaline urine containing a

tion of common fatty acids can proceed no further than the formation of acetoacetic acid. This acid and its decomposition products β hydroxybutyric acid and acetone therefore accumulate in the blood to produce an organic acidosis. It is now believed rather generally that the influence of carbohydrate

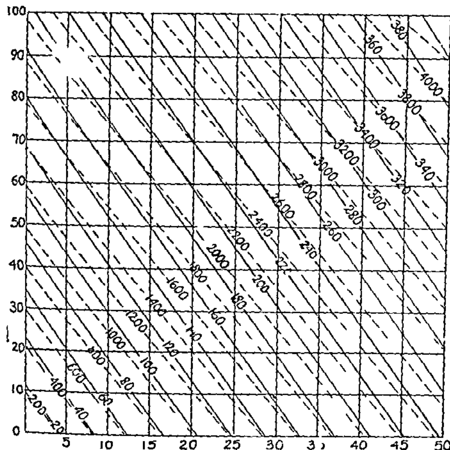


FIG 4.—Graphic chart for the estimation of Shaffer's ketogenic antiketogenic ratio. Abscissa = carbohydrate in gms. Ordinate = protein in gms. Continuous diagonal lines = fat in gms. Broken diagonal lines = Calories.

If any two of these factors are known the amount of the two others necessary to give a ratio of 2/1 can be estimated. For example, if it is desired to give 40 gms. of carbohydrate and 60 gms. of protein it will be found that the corresponding lines intersect at a point that indicates about 290 gms. of fat and 3100 calories.

In order to prevent ketosis then with a diet containing these amounts of carbohydrate and protein one must give not more than 290 gms. of fat and can not attain more than 3100 calories.

in furthering the combustion of fat involves reactions between the two substances that follow stoichiometric laws. Shaffer[52] calculates that each molecule

majority of patients with heart failure it is modified or masked by other electrolyte disturbances perhaps connected with retention of salt and water, and edema formation. In pneumonia carbon dioxide excess, if it occurs, is also masked by the effects of temperature and possibly other factors.

Excess of Acids Other Than Carbonic

If mineral acids or acidifying salts of these acids such as ammonium or calcium salts are administered to an individual, bicarbonate is at once broken down to provide base for the neutralization of the new acid, and carbonic acid is liberated.[13] The $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio and pH both tend to diminish. The extent to which they change depends on the amount of acid and the speed with which it is given. If small amounts are given slowly, the respiratory system may be able to keep the pH constant. If the quantity of acid is large, and especially if it is rapidly administered ratio and pH both fall. In any case blood bicarbonate is diminished. Probably other acids also yield base if the need is great enough.

Ultimate compensation is established by means of the kidney. The urine becomes acid and phosphate and ammonia excretion are augmented.[26f] In spite of these defenses an excess of base is usually lost in the urine and with this base a proportional amount of water.[20f]

Similar disturbances follow the metabolic production of more than the usual quantities of organic acids or the peroral administration of organic acids that can not be oxidized by the body. The commonest conditions in which excess of acid occurs are exercise and carbohydrate starvation.

During severe exercise lactic acid is produced more rapidly than it is burned, and its concentration in the blood, therefore increases.[6,39] Being a stronger acid than carbonic it takes base from bicarbonate and frees carbonic acid just as a mineral acid would.[41,48b] Presumably it may also displace Cl but no reduction of blood Cl has been observed in exercise. On the other hand Peters, Bulger, Eisenman and Lee[48f] noted an increase of base in the blood plasma of the exercised limb. As soon as exercise ceases the lactic acid is burned up, and the base liberated by it combines with carbonic acid again thus restoring normal conditions.

The Organic Acid Excess (Ketosis) of Carbohydrate Starvation

For the complete oxidation of fatty acids in the human organism the simultaneous oxidation of carbohydrate is necessary. If carbohydrate is not provided in the diet or if the organism is incapable of burning carbohydrate the oxida-

excess depend directly on the degree of impairment of carbohydrate metabolism and the rate of metabolism In the mildest cases of diabetes the concentration of ketone bodies in blood and urine may remain unaltered In slightly more severe cases moderate ketonemia and ketonuria may appear without any appreciable alteration of the acid base equilibrium In moderately severe cases disturbances quite similar to those found in the acidosis of total starvation are observed

In most severe diabetic acidosis profound alterations of the whole electrolyte picture are encountered The carbon dioxide of the blood may fall to less than 10 volumes per cent (less than 5 milli-equivalents of bicarbonate) and in spite of the most extreme hyperpnea the respiratory system may fail to prevent the pH of the blood from falling Plasma pH values as low as 6 9 and 7 0 have been reported Chloride also fails to afford more base for the neutralization of the surplus organic acid Presumably in most cases this chloride is lost in the urine in great part but it may be merely transferred to the tissues The urine becomes highly acid and urinary ammonia enormously increased Diuresis is profuse and with the overventilation leads to extreme dehydration which is evidenced by hemoconcentration Depletion of the total base content of the body inevitably ensues even if the concentration of base in the blood remains unchanged If the condition is prolonged the defensive mechanisms may fail even to maintain the normal base concentration and total electrolyte deficiency occurs[45]

Therapeutic Indications in Organic Acidosis

The therapeutic indications in organic acidosis are clear First of all the combustion or removal of the organic acid must be promoted In starvation this can be effected by the administration of carbohydrate in diabetes by the administration of insulin and carbohydrate Water must be given in large quantities to overcome dehydration and with it salt enough to restore the base deficit If water alone is given either it will not be retained or else a reduction of the total electrolyte concentration of the blood will result Sodium chloride is the most rational salt to use because it contributes both base and the most important acid of blood and tissues both of which have been depleted Bicarbonate is seldom necessary The base liberated by the combustion of the ketone acids under the influence of insulin is almost always sufficient to restore the normal blood bicarbonate concentration[1] In fact it is not unusual to see a true bicarbonate excess after recovery from ketosis even if no bicarbonate is given[21, 45d] The administration of additional bicarbonate tends only to accentuate this tendency to alkalosis The development of alkalosis moreover is not entirely harmless It is at least a contributory cause of diabetic edema

of glucose reacts with two molecules of diacetic acid Although slight degrees of ketosis are often observed in patients who are burning sufficient carbohydrate to satisfy the requirements of Shaffer s ratio, severe ketosis has been observed only when the metabolic mixture has exceeded this ratio Figure 4 presents a chart by which diets, which conform to the Shaffer ratio can be rapidly estimated

Shaffer s equation from which this chart is derived is

$$\frac{\text{Mols fatty acid}}{\text{Mols glucose}} = \frac{2}{1} = \frac{3\ 43\ \text{fat} + 2\ 40\ \text{protein}}{0\ 57\ \text{fat} + 5\ 56\ \text{carbohydrate} + 3\ 04\ \text{protein}}$$

in which fat protein and carbohydrate are expressed in grams and the numerical coefficients are factors for the conversion of these values to mols of fatty acid and glucose

In total starvation ketosis (that is the accumulation of diacetic and β hydroxybutyric acids and acetone in the blood and their excretion in the urine) does not develop at once because the body possesses a limited reserve of carbohydrate in the form of stored glycogen, which enables it to oxidize fatty acid for a while Even after this is exhausted, the production of ketones seldom becomes very great because a certain amount of carbohydrate formed from protein permits the combustion of some fat *

The acid base equilibrium changes usually observed in the ketosis of total starvation [9d] are 1 The appearance of ketone acids in the tissues, blood and urine 2 Reduction of blood bicarbonate and liberation of carbonic acid 3 The respiratory response is usually adequate and prevents any serious reduction of blood pH 4 Excretion of an acid urine with an unusually large amount of acid phosphate and ammonia and ketone bodies 5 There is, besides a diuresis with loss of a proportional amount of sodium from the body fluids 6 Finally because of the destruction of tissue which is necessitated by the lack of other food an excess of potassium also appears in the urine There is then a diminution of the total base content without any change in the total base concentration in the body

In diabetes mellitus [45d] the ability of the organism to oxidize carbohydrate is impaired The degree of impairment may vary from a mere inability to burn unusually large amounts of carbohydrate to a complete diabetes when every substance capable of being transformed to sugar in the body is so transformed and excreted in the urine as glucose In the latter case every molecule of fatty acid produced in the processes of metabolism goes to form ketone bodies The quantity of ketone acids formed and therefore the degree of organic acid

* Gamble Ross and Tisdall [9d] have shown that during total starvation sufficient protein is burned to prevent the development of a dangerous degree of ketosis and from Shaffer s formula it can be seen that slightly more than enough glucose is formed from protein to permit combustion of the fatty acid derived from the same source

of alkali are rapidly administered respiration is not always inhibited * and therefore change of pH is not prevented. The total electrolyte and base concentration is rapidly restored, chloride apparently yielding its place to bicarbonate.[22, 49] A shift of chloride to the tissues, which this change suggests, is contrary to the theoretical considerations advanced above. Alkalinization of the blood should cause a transfer of water and chloride from blood and tissue cells to serum and lymph. If hemoglobin, cell volume and plasma proteins are determined as well as electrolytes, it is found that their concentrations fall after bicarbonate administration, indicating dilution of the blood.[45f] The reduction of chloride is not due, then, to the excretion of Cl in the urine nor to its transfer to the cells, but is due merely to dilution of the blood as it were by an isotonic sodium bicarbonate solution. This dilution of course mitigates the alkalinizing effect of the bicarbonate and must be considered as a compensatory reaction. Other minor intrinsic beneficial reactions are the production of ketone and lactic acids. Normal electrolyte equilibrium is ultimately established by the secretion of an alkaline urine containing bicarbonate, and the suppression of ammonia excretion.[13] *It should be obvious that the real indication for bicarbonate therapy is deficiency of base without corresponding depletion of any acid other than carbonic.*

The administration of neutral salts will also cause base excess and alterations of acid distribution. For example, after large amounts of sodium chloride solution there may be a transitory increase of both base and Cl in the plasma. The base rapidly returns to the normal level while Cl continues high somewhat longer, bicarbonate falling an equivalent amount. The end result at first sight resembles that following administration of hydrochloric acid or ammonium chloride. In point of fact the effects of sodium chloride and hydrochloric acid are quite different. The latter reduces bicarbonate by displacing it from combination with base; the reduction caused by the neutral salt is entirely due to dilution.

Deficiency of Acids Other Than Carbonic

Just as it has been shown that excess of any one acid in the blood is met by reduction of one or more of the other acids, so a deficiency of one acid leads to the retention or production of other acids to restore equilibrium. Although each one of the acids found in normal blood probably serves a special function, nevertheless, within limits, to stabilize osmotic and acid base equilibria the

* Without discussing the various theories that have been advanced to explain the failure of the respiratory system to respond and at the risk of being accused of arguing teleologically, the author can not help pointing out that this absence of respiratory response is advantageous to the organism. Apnea might well restore the acid base equilibrium at the expense of life by preventing the supply of oxygen to the tissues.

Furthermore there is some evidence that alkalosis interferes with the oxidation of carbohydrate At least, it is clear from the discussion above that it may be a cause of ketosis

Occasionally, but rarely, a case presents such extreme depletion of base that bicarbonate administration is necessary In this case, after ketosis has been entirely eliminated and plasma chloride restored to the normal level, bicarbonate and total base will remain low

Bock Field and Adair [9], and Starr and Fitz [5] have reported cases in which, after ketosis had cleared up organic acid excretion remained high and blood bicarbonate low They believe that in these instances diabetes was responsible for the overproduction of non ketone organic acids and advocate the use of bicarbonate to combat this organic acidosis Severe diabetic acidosis is usually provoked by some complicating condition, and the latter, rather than diabetes itself may have been responsible for the appearance of the unidentified organic acids But in any case, the administration of bicarbonate is not, as we shall see in the following section an efficient method of combating organic acidosis

Organic acid excess of unknown origin and nature has been observed in certain cases of pneumonia, nephritis and miscellaneous pathologic conditions

Excess of Base in the Blood

An excessive concentration of base in the blood can not occur unless it is balanced by an equivalent excess of acids, and even then is extremely rare because accumulation of base is usually attended by retention of a proportional amount of water Nevertheless one occasionally finds especially in nephriti high base concentrations in the blood with balanced increases in chloride and bicarbonate or more rarely abnormally large amounts of organic acid chloride or bicarbonate [44] The cause and significance of these pictures is not clear The high chloride picture conforms to what Ambard Blum and others have called dry chloride retention In the author s experience it is usually a transitory condition, characteristic of a certain stage rather than a type of nephritis

Base excess can be produced experimentally by the administration of alkalies such as hydroxides carbonates and bicarbonates of potassium and sodium The hydroxides and the carbonates are rapidly converted to bicarbonates in the body by reaction with carbonic acid $NaOH + CO_2 = NaHCO_3$ $Na_2CO_3 + CO_2 + H_2O = 2NaHCO_3$

The administration of these substances increases the base and the bicarbonate as well as the $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio and the pH of the blood [13] If large amounts

the administration of both salt and water and not water alone is indicated To the causes of dehydration mentioned above may be added fever, vomiting and diarrhea

In uncomplicated total electrolyte deficiency base chloride and bicarbonate are all proportionally reduced even though the acid base equilibrium is essentially undisturbed

Vomiting and Obstruction of the Alimentary Tract

From consideration of the preceding sections it should be evident that vomiting may affect the acid base equilibrium in a variety of ways 1 by producing dehydration 2 by interfering with feeding and therefore causing starvation acidosis 3 by loss of chloride as hydrochloric acid in the vomitus 4 by loss of salt in the vomitus causing total electrolyte deficiency

If the vomiting is only occasional what little effect it may have is entirely made up in the free interval If it is persistent or continuous all the disturbances listed above occur in varying degree and the end result depends on which factor predominates The most striking pictures of the effects of vomiting on electrolyte equilibrium are encountered in patients with obstruction of the alimentary tract and especially at the pylorus In these cases loss of hydrochloric acid in the vomitus causing reduction of blood Cl is usually the most characteristic feature [0f 21] Bicarbonate increases as Cl falls by the combination of CO with the base liberated by the chloride In consequence the $\frac{[NaHCO_3]}{[H_2CO_3]}$ ratio and pH tend to rise and tetany often results The bicarbonate increase is always mitigated and may be entirely prevented by the substitution of ketone acids caused by starvation[20] The vomitus invariably leads to dehydration and base depletion follows Part of the base is lost in the urine but the vomitus itself besides hydrochloric acid contains a certain amount of neutral salt In some case especially when the HCl concentration of the gastric contents is not great there may be an actual diminution in the base concentration as well as the base content of the serum[49f]

The urine in cases of pyloric obstruction usually becomes alkaline containing large amounts of bicarbonate and minimal quantities of ammonia and chloride[20 49f] *

Obstruction of the alimentary tract at other points than the pylorus causes similar changes all of which can probably be ascribed to deprivation of food and fluids and the added effects of vomiting Haden and Orr[21] have indeed

* Hartmann Scott and Moser (30) found acid urines in certain cases with high serum CO In these instances the reduction of serum Cl was greater than the increase of CO₂ The obvious inference is that there was an organic acid (probably ketone acid) excess or a deficit of base The administration of NaCl to these patients rendered the urine alkaline

relative concentrations of all or almost all of them may be altered That chloride may replace bicarbonate has already been pointed out It has been shown also that in the recovery from diabetic acidosis carbonic acid may take the place of organic acids which had previously displaced chloride

The gastric secretion of hydrochloric acid removes from the blood a certain amount of chloride This has a demonstrable effect on the blood electrolytes and acid base equilibrium [1] Normal individuals, after a meal, show a slight reduction of the Cl of serum with a proportional rise of HCO_3[1] and secrete a more alkaline urine [1, 3] These alterations are exaggerated in patients with hyperchlorhydria and diminished or absent in those with hypochlorhydria or achlorhydria [30] Changes of the same character, only more profound, are produced by vomiting These will be discussed at more length in a subsequent section

Deficiency of Base (Total Electrolyte Depletion)

It has already been shown that a deficiency of base may occur in various types of acidosis always associated with some alteration of the relative proportions of the different acids in the blood It is, however, possible to reduce the concentration of base in the blood without essentially altering the acid base equilibrium Such reductions are usually attended by serious symptoms

Rowntree [50] found that the administration of excessive water to dogs by stomach tube produced serious intoxication resulting sometimes in convulsions and death These symptoms were relieved by the administration of salt and did not appear if equal amounts of saline solution were given instead of water It may be inferred from this that the intoxication was due to reduction of the electrolyte concentration of the blood rather than to the increase of the water content of the body Similar states of intoxication are occasionally observed in patients who have received excessive amounts of fluid without salt, especially when urine secretion is impaired and the water is retained In a case of this kind Peters Bulger Eisenman and Lee [43] found the concentration of plasma proteins and electrolytes greatly reduced

It is apparently easier to induce this condition in patients who have suffered dehydration and salt depletion Moss [46] found that men doing heavy labor at a temperature of 98 to 10 °F lost large quantities of both water and salt by sweating If they then drank plentiful amounts of water they developed miner s cramps The latter could be prevented or relieved by the administration of salt

It is, then inadvisable to give more water than the excretory organs can dispose of, without also giving some salt To combat dehydration, which is almost always accompanied by depletion of the total salt content of the body,

glomerulonephritis of the Volhard-Fahr classification or chronic parenchymatous nephritis of the older terminology the base concentration is usually normal or slightly reduced, seldom appreciably elevated[4 1 45f] One may infer that retention of salt is attended by a proportionate retention of water Blum[45] and others[15] have shown that sodium salts are more prone to increase edema than corresponding potassium salts which may even induce diuresis This may indicate that the hydrophilic tendency is largely confined to the interstitial fluids and does not affect the cells to the same extent

Although base concentration is usually normal the concentrations of the acid are often disturbed The commonest alteration of the normal relations is an increase of the sum [HCO_3] + [Cl] perhaps to satisfy the base usually combined with the plasma proteins which are greatly reduced in this condition[45f] Sometimes bicarbonate but more often chloride[6b 45f] plays the predominant rôle in this increase In fact [Cl] may be so high as to force a recession of bicarbonate In the latter case one might speak of the condition as a hydrochloric acid acidosis The pH of the blood in any case is little altered and the character of the urinary acids and bases is comparatively normal In most instances the edema is aggravated by the administration of alkali while acidifying salts such as ammonium chloride or calcium chloride often promote diuresis[6]

In the types of nephritis associated with high blood pressure retention of nitrogenous waste products and the development of the uremic syndrome the arteriosclerotic kidneys and chronic interstitial nephritis of the earlier classifications reduction of blood bicarbonate is often seen in the terminal stages of the disease frequently attended by reduction of blood pH Numerous explanations of this acidosis have been offered no one of which is entirely satisfactory Marriott and Howland[43] first suggested that it was due to retention of phosphate because they found the inorganic phosphate of the blood high in these conditions Bulger Peters Eisenman and Lee[48] and others[4] have shown that the increase of phosphate is far too small to account for the bicarbonate change and that the two disturbances do not parallel one another Fetter[18] found that the administration of alkaline sodium phosphate Na_2HPO_4 restored the normal bicarbonate concentration and augmented urinary phosphate excretion without altering the concentration of phosphate in the serum Finally Boyd Courtney and MacLachlan[10] have shown that the hyperphosphatemia of nephritis in children at least is attended by no diminution of urinary phosphate excretion In fact they observed negative phosphate balances in many instances

Sometime as in the edematous cases chloride is found abnormally high but this is a comparatively rare event More often chloride like bicarbonate is low Not infrequently bicarbonate is high with chloride proportionately

claimed that the reduction of chloride is the result not of vomiting but of the transfer of Cl to the tissues to neutralize toxic substances absorbed from the obstructed gut. There is little to support such a theory. Gamble [0] has shown that the loss of hydrochloric acid in the stomach contents after pyloric obstruction is quite great enough to account for the changes of blood electrolytes. Foster and Hausler [19] found that dogs with experimental intestinal obstruction could be kept alive for the first few days after operation only by the parenteral administration of sodium chloride. The amount of chloride required depended on the amount lost in the vomitus. Later the administration of chloride could be discontinued without danger and the animals lived for considerable periods without symptoms, succumbing finally to the effects of starvation and water deprivation. During this latter period the dogs did not vomit and showed no tendency to develop hypochloremia. Miller [4] found that rabbits, who can not vomit, excreted large amounts of hydrochloric acid and water into the stomach during the first fifteen hours after pyloric obstruction. If, at the end of this time the obstruction was removed, the contents of the stomach were again absorbed and the animals recovered. If, however, the stomach contents were removed, termination of the obstruction did not save the animals, even if the stomach contents were replaced by an equal amount of water. Finally, Haden and Orr [24] themselves have been unable to demonstrate any transfer of Cl to the tissues. In fact they have found low chloride concentrations in both muscle and liver of dogs with obstruction of the alimentary tract.

Besides operative removal of the obstruction, treatment should, of course, consist in the parenteral, preferably subcutaneous, administration of enough normal saline to overcome the dehydration and to restore the base and chloride concentrations in the blood to the normal level and enough glucose in addition to prevent ketosis.

Electrolyte and Acid-Base Disturbances in Nephritis

In spite of the tendency to salt retention which so frequently accompanies nephritis, increased base and total electrolyte concentration in the blood is seldom encountered in this condition [14, 22, 4, 4, 48, 4]. When it does occur, it seems to be, as has been pointed out above, rather a mark of a certain stage of the disease than a characteristic of any special type of nephritis. Total base excess is no more often observed in the presence of edema than in non-edematous conditions. In fact, in the author's own studies it occurred most frequently in non-edematous chronic nephritis without uremia.

In the types of nephritis which are characterized by a tendency to edema, without hypertension or retention of nitrogenous waste products, but with low serum proteins and profuse albuminuria, the nephrosis or nephrotic type of

dyspnea vomiting occasionally diarrhea and diuresi The inability of the kidney to form ammonia to which Van Slyke and his associates [71] and Rabino witch [80] have called attention may al o force the organism to excrete a larger quantity of the more essential bases to neutralize the acid produced in metabo li m especially if as is not improbable the production of such acid in uremia is excessive The ability of the kidney to excrete an acid urine eems to be one of the last functions retained in nephritis [71]

The acidosis of nephritis then for this term has been generally employed to describe the observed bicarbonate deficiency is a product of a variety of

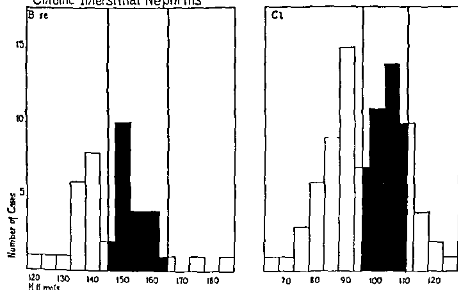


FIG 6 — Base and chlori I concentrations in the serum of a series of patients with chronic interstitial nephriti Values within th limits of normal variation are indicated by the solid black columns

disturbances of which the chief is probably total ba e (or total electrolyte) deficiency Chloride excess is a rare contributory factor more often there is a concomitant chloride deficit Organic acid accumulation may be important but is u ually like hyperpho phatemia a minor factor

The therapeutic indications seem to be 1 To prevent or check vomiting and other symptoms which promote dehydration without aiding in the secretion of urine which alone can eliminate those ubstances retention of which provokes the nephritic toxemia 2 The administration of enough food and e pecially carbohydrate to reduce nitrogen metaboli m and organic acid production 3 Administration of large amounts of fluid and sodium chloride to overcome

reduced In most instances the sum of [Cl] + [HCO_3] is distinctly below normal Vomiting a frequent symptom in this condition, is, if not the only cause at least a contributory cause of the hypochloremia Starvation, a result partly of the vomiting, may also explain, in part the increase of organic acids in the blood in the terminal stages of uremia[49c]

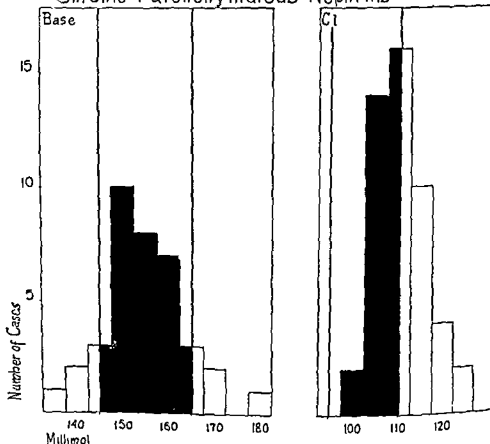


FIG 5 — Base and chloride concentrations in the serum of a series of patients with chronic parenchymatous nephritis Values within the limits of normal variation are indicated by the solid black columns

One of the most important factors in the production of the bicarbonate deficiency however is depletion of the base of the blood The concentration of base in the serum in the terminal stages of uremia is usually appreciably and often extremely reduced[4, 48] This is of course an indication of total electrolyte deficiency Several factors probably contribute to this deficiency, which is as usual associated with dehydration Among these may be mentioned

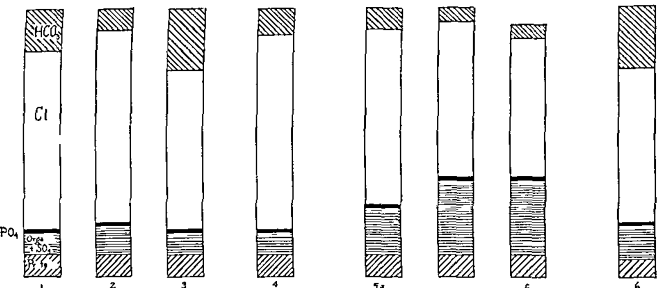


FIG 7 — 1 Represents the relative concentration of the acids in normal blood In the succeeding columns each acid is represented in the same manner and on the same scale Changes in the total height of the column therefore indicate changes of base concentration Change in the height of the column representing an individual acid indicates a change in the concentration of that acid

2 *Primary carbon* dioxide deficiency due to overventilation $[HCO_3]$ diminishes while [Cl] and organic acids increase.
3 Primary carbon dioxide excess of emphysema $[HCO_3]$ increases at the expense of [Cl]
4 Mineral acid excess due to ammonium chloride *[Cl] increases at the expense of* $[HCO_3]$
5 Organic acid excess Ketosis of diabetes a) Mild Organic acid increased at expense of $[HCO_3]$ only b) More severe $[HCO_3]$ and [Cl] both displaced by ketone acids c) Extremely severe Total base deficiency as well as reduction of both $[HCO_3]$ and [Cl]
6 Effect of bicarbonate administration $[HCO_3]$ increased Some increase of organic acid Reduction of [Cl] by dilution of blood The latter is indicated by protein reduction

dehydration and electrolyte deficit Edema in these cases is rare and usually due to cardiac failure If cardiac action can not be maintained the outlook is hopeless It can not be bettered by restriction of fluids and salt 4 Bicarbonate is of value only to allay the dyspnea of acidosis when this appears 5 Little benefit can be derived from diuretics other than digitalis The latter is an invaluable aid when, because of failing heart action the production of an adequate urine volume can not otherwise be secured Acidifying diuretics and especially ammonium chloride which has been recommended are distinctly contraindicated They can only aggravate dehydration and base deficit Besides this both ammonia and urea into which it is largely converted in the body, are excreted with difficulty by the chronic nephritic kidney

Figs 5 and 6 show statistically the concentrations of base and chloride in the serum of a series of nephritic patients studied by the author and his associates They show the relative infrequency of base excess in all types of nephritis and the frequency of base deficit in the chronic interstitial type They also demonstrate the fact that chloride excess is not uncommon in chronic parenchymatous nephritis while hypochloremia is almost the rule in the chronic interstitial form of the disease It must be added that both base and chloride deficits occurred only in patients with profound disturbances of renal function usually frank uremia

Conclusion

For those who find graphic representation an aid to comprehension Figures 7 and 8 have been provided In these the author has tried to illustrate the nature of the disturbances of serum electrolyte concentration which occur in the conditions which have been decribed in detail above All the figures have been drawn to the same scale and only the acids have been represented As the sum of the acids must equal that of base it is obvious that the height of the whole column is a measure of the total base as well as the total acid of the blood

In closing the author wishes to offer certain apologies In order to condense so much material in such a small compass it has been necessary to neglect some aspects of the subject in order to emphasize others In the selection of material for emphasis clarity and continuity have been the chief aims On most controversial points it was essential for the sake of brevity to make a decision or remain silent An attempt has been made to distinguish between fact and inference Finally references to work from the author s own laboratory and this too often unpublished and therefore not available to his readers, are all too frequent He can only plead that equally complete data from any other sources were in many instances unavailable or more rarely differed from his own In the latter case he must be excused for reasonable confidence in his own work

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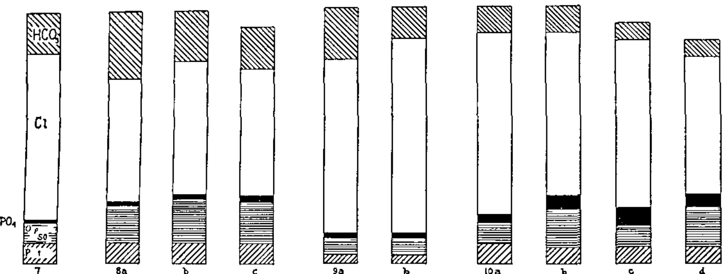


FIG 8 — 7 The relative concentrations of the acids in normal blood

8 Different effects of pyloric stenosis a) Reduction of [Cl] and replacement partly by organic acid but chiefly by [HCO_3] b) Reduction of [Cl] with more organic acid production and therefore less increase of [HCO_3] c) Reduction of total base and [Cl] with increase of organic acid and little increase of [HCO]

9 Commonest changes encountered in chronic parenchymatous nephritis a) Response to protein reduction by increased [Cl] and [HCO_3] b) [Cl] excess with slight reduction of [HCO_3] as well as low proteins

10 Commonest changes encountered in chronic interstitial nephritis with uremia and acidosis a) High [PO_4] and [Cl] with reduction of [HCO_3] b) High [PO] and organic acid with low [HCO] c) Total reduction of base and [HCO] with increase of [PO_4] d) Reduction of base [Cl] and [HCO_3] with increase of [PO_4] and organic acid

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CHAPTER VII

RADIATION AND ITS EFFECTS

By George W Holmes

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Historical

Although the use of light in the treatment of disease is nearly as old as the history of medicine, radiology as a specialty in medicine is of comparatively recent origin The discovery of the roentgen ray was announced by William Conrad Roentgen on December 28 1895 when he presented his communication Ueber eine neue Art von Strahlen' to the President of the Wurzburger Physicalisch Medicinische Gesellschaft Radium ray was first observed by H Becquerel in 1896 and the discovery of radium was announced by Madame Curie in 1898 The ultra violet ray was discovered by Rieter in 1901 Since this time a matter of a little over fifty years radiology has established for itself an important place in the diagnosis and treatment of disease There has developed around its use an extensive literature both in the field of medicine and of physics, and physicians trained in radiology are now recognized as specialists in a new field of medicine

Probably no scientific discovery in modern times was accepted more promptly by the medical profession than that of the roentgen rays Two weeks before Roentgen publicly announced his discovery it was generally known throughout the civilized world and many articles had appeared in the lay press Before the first year had elapsed many papers on its use in medicine and surgery had been presented and even a book had been published Among these early publications was one by Francis H Williams of Boston read before the Association of American Physi

cians at its eleventh annual session, April 1896 In this paper Dr Williams described the appearance on the fluoroscopic screen of an enlarged heart, of the chest in a case of lobar pneumonia and in two cases of pulmonary tuberculosis

Within the first decade most of the important problems connected with the use of x-ray in medicine and physics had been studied to some extent, and an enormous amount of research work had been done Hermann Gocht lists 125 books on this subject before the year 1905 The acceptance of roentgenology as a method of diagnosis in the general practice of medicine, however, was much slower Osler's Practice of Medicine, published in 1905, gives scant data on this subject, there is no mention of the words "x-ray" or 'radium" in the index, and they are mentioned only twice in the text In the fifth edition of DaCosta's Modern Surgery, published in January 1907, the text contains only brief mention of the x-ray under the headings of "stones in the kidney" and diseases of the bones and joints" There is also brief reference to a possible beneficial effect from the use of x-ray in the treatment of sarcoma carcinoma, lymphadenoma and certain diseases of the skin

The failure to make use of the roentgen-ray in medicine early was due largely to the unsatisfactory apparatus then available for the production of the ray The long exposures necessary to secure good negatives resulted in blurring of the shadow cast by moving organs and in the production of plates which were of little value in diagnosis During the next ten years there was a marked improvement in x-ray apparatus including the introduction of the mechanical rectifier in 1907 and of the Coolidge tube in 1913 This advance in the quality of the apparatus paved the way for rapid progress in the general use of the x-ray in medicine and surgery The use of opaque substance within the body cavity was suggested and tried early in the first decade The bismuth meal for x ray examination of the gastrointestinal tract in animals was described by Cannon in 1898 and in man by Williams and Cannon in 1902 The possibility of injecting the kidney pelvis with opaque substance for the production of cystograms was shown by Voelcker and Lichtenberg in 1905 The introduction of substances within the body cavities, both opaque and non opaque, has increased considerably the field of roentgen diagnosis Among the most important of these is the use of air within the ventricles of the brain, direct ventriculography, first advocated by Dandy in 1918, and in 1919 encephalography introducing air by way of the spinal canal This method has greatly increased the accuracy of

diagnosis in tumors of the brain and its cavities Air and various other gases have been introduced into the peritoneal cavity to make visible the liver kidney, spleen and various abdominal tumors this method was first described by Weber in 191. and later by Stewart in 1914 The development of the iodized oils by Sicard and Forester in 19 1 and the discovery that these substances could be injected into the bronchial tree or into the spinal canal without danger of injury led to advances in the diagnosis of obstructing lesions of the bronchi and to the early demonstration of spinal cord tumors In 19,0 Ritschow showed that certain substances could be used to demonstrate blood vessels and in 1938 Robb and Stein berg using this method were able to demonstrate the chambers of the heart and the great vessels of the thorax

Another development of the use of contrast substances has been brought about through the injection into the blood stream of substances containing a halogen compound which are excreted later either by the liver or kidneys A method of examining the urinary tract based on this principle was first described by Von Lichtenberg in 19 1 and Cole in 19 3 developed a similar procedure for examining the gall bladder

At no time in its history has roentgenology advanced more rapidly than in the past ten years with its use almost any organ of the body may now be studied

In the field of therapy a corresponding advance has been made With the development of the Coolidge tube and of machines capable of producing rays of extreme short wave length approaching the gamma rays of radium the administration of large doses of irradiation to deep seated tumors has been made possible

The superficial effects of the roentgen ray on living tissues were observed early Edison and others noted its effect upon the eyes in 1896 and in the same year Elihu Thompson of Boston published his classical experiments carried out on his own skin showing that not only were these rays capable of producing an erythema but that the effect was cumulative and that there was a latent period Furthermore he called attention to the possible seriousness of these injuries and suggested methods of protection Unfortunately Thompson s work did not receive wide publication and was not generally accepted by the medical profession or those using the roentgen ray That most of the serious injuries which the early workers received could have been avoided had they heeded Thompson s warning is shown by the case of his life long friend Francis Williams who did accept the warning and who although he used the

fluoroscope perhaps more than any other worker during the early days showed no evidence of injury from the rays, up to the time of his death at the advanced age of 84 Thompson was not a physician, and his first paper was not published in a medical journal, but in the light of present knowledge it was perhaps the most important publication of the period and should convince one of the importance of reviewing the literature in allied as well as that of one's specialty

In 1902 E A Codman was able to collect 170 cases of injuries from the roentgen rays in half of which the injuries were serious Although cause effect and method of protection have been well known since that time injuries continue to occur

The fact that epilation may follow exposure to the roentgen ray led to its logical use in treatment On April 10, 1896 J Daniels of Vanderbilt University reported that he "caused the hairs to fall from the head of a colleague whose skull he had 'photographed with x rays' " Other similar reports appeared in the American and European literature Leopold Freund of Vienna reasoned that the rays could be used to remove hairs for therapeutic purposes, and on January 15 1897, at a meeting of his local medical society, he reported having treated a patient with a hairy naevus Freund was probably the first to use the rays on a basis of a known biological effect, previous usage having been entirely empirical Following the publication of his report the treatment of superficial lesions with the roentgen ray became general and it was tried out in a great variety of conditions Among those who published reports and who are generally credited with priority are Freund hypertrichosis 1897, Kummell and Schiff lupus, 1897 Ziemssen psoriasis, 1898, Freund sycosis and favus 1898, Jutassey, vascular naevus, 1898 Hahn, chronic eczema, Sjogren and Stenbeck, epithelioma 1899, Schultz, mycosis fungoides, 190 Pusey and Senn, leukemia and lymphadema 1903 Francis Williams book 'The Roentgen Rays in Medicine and Surgery' appeared in 1901 and may be considered as having laid the foundation of radiology in American medicine The early investigators recognized the importance of determining the dosage required to bring the desired biological effects about In the early apparatus (machine) there was almost complete absence of energy control and dosage could be determined only by fluoroscopic observation of the operator's hand a practice which all too often led to serious injuries The perfecting of the spark gap and of the milliampere meter were early steps toward the control of dosage The fact that certain substances changed in color when exposed to the ray was utilized also in developing a measure of dosage, among the best

known of these was the chromoradiometer of Sabourand and Noise and the quintimeter of Kienbocl In 190 L Benoist described a penetrometer — a device for measuring quality of radiation based on the rate of absorption in different thicl nesses of metal None of these forms of measurement was entirely satisfactory and it was not until Duane and others developed a method of determining dosage by using the ionizing properties of the roentgen rays that a satisfactory technique was established

Knowledge of the effect of radiation on living tissues has also passed through many phases but on the whole it has shown a steady growth In 1903 H Alber Schonberg announced that aspermia could be produced in experimental animals by exposure to the roentgen ray, and in the same year H Heinl e found what seemed to be a selective action of the rays on the lymphoid tissues of animals and suggested their use in the treatment of diseases of the lymphatic system In 1904 J Bergonie and L Tribondeau completed their histolgical studies on the radiated testicles of rats and formulated a law since known as the law of Bergonie and Tribondeau which forms the basis of the present knowledge of the effect of radiation on all living tissues It is as follows Immature cells and cells in an active state of division are more sensitive to radiation than are cells which have already acquired their adult morphologic and physiologic characters

With the recognition that sterilization could be produced by radiation and that it was not always permanent, there arose the question of its effect on heredity In 1906 Bardeen an American anatomist showed that the fertilized ova of the toad when exposed to radiation exhibited abnormalities in development, and he concluded that the action of the ray must be on the unknown substances in the nucleus which control the morphogenic activities of the cells As early as 190 C L Sl inner suggested that the beneficial effects of the roentgen rays in the treatment of tumors was due in part to the inflammatory reaction which developed in the surrounding tissues Later Ewing established the fact that the development of fibrosis in radiated tissues encapsulated the remaining cells and that this process with the sclerosing and narrowing of the lumen of blood vessels prevented their further growth for long periods of time This work of Ewing laid the foundation of the present technique in the management of inoperable malignant tumors and led to the dictum that to remove surgically residual tumor masses after heavy radiation was unwise During the years 19 0 to 1935 extensive investigation into the effect of different wave lengths and of the time factor was

carried out The writings of Charles Packard, which appeared during this period are perhaps the most complete of those published in the English language As a result of all this experimental work the following facts were established (1) that the biologic effects of x rays with the range of wave lengths now in use, is the same, (2) that no stimulating effect can be produced with this type of radiation, and (3) that the shorter the time in which the total amount of radiation is given the greater the effect

That the effect of a given time factor is not the same on all cells was shown by Regaud in 19[illegible]2 He was able to destroy completely radiosensitive cells without causing serious injury to surrounding less sensitive cells by subjecting the tissue mass to prolonged exposure with radiation of low intensity As a result of this experimental work he developed a new method of treatment in which the exposure time was based on the sensitivity of the tissues being irradiated Another recent discovery of considerable importance was made when x-rays of very short wave length such as those produced at voltages produced at 1[illegible]00 KV or over and the radium bomb, became available The maximum effect of this kind of radiation was found to be below the skin surface due to the relative absence of back-scattering, thus permitting a large depth dose without skin injury

Radium was discovered by Pierre and Marie Curie in 1898 The development of its use in medicine was along the same line as that of the roentgen ray and will not be discussed here Its effect on normal and pathological tissue is also the same, and its use is governed by the same laws The only difference is in the way in which the radiation is produced and the fact that other forms of radiation are present except when heavy filters are used The principal advantage of radium over other forms of radiation lies in the fact that it may be inserted into body cavities or even directly into the tissues in or about a tumor The development of new methods of producing radio active isotopes in large quantities offers still another means of attacking malignant tumors that may be of far reaching importance

The Effect of Radiation on the Individual Cell and Upon More Complex Organism

The therapeutic use of the roentgen ray and the rays of radium is dependent upon the fact that they are destructive to living tissue and that this effect varies according to known laws the most important of which

have to do with the embryological origin of the tissue its rate of growth the amount of radiation it receives and the time in which the total dose is given There is no difference in the selective action of the various wave lengths in so far as is known at the present time

The effect of radiation is both immediate and remote Change in the appearance and behavior of the individual cell may occur within a few minutes after they are exposed but gross changes usually are not observed until weeks months or even years have passed On the individual cell the first step in the series of changes is purely physical The quanta of radiation collide with electrons of the atom composing protoplasm and displace them from their normal position in the system or remove them altogether The atom is no longer the same a chemical change has taken place and as a result the morphological and physiological condition of the cells is altered This effect does not appear at once and may not be observable for some hours or days The protoplasm of the cell becomes cloudy and swollen later vacuoles appear in it In the nucleus the chromosomes are clumped and shrunken In cells which are undergoing mitosis at the time of exposure the effect is greater than in resting cells Mitosis is not stopped but the arrangement of the chromosomes is altered and the cells usually die after mitosis is completed Everything which increases the rate of cell division increases the effect of radiation anything which retards cell division decreases it In general when living cells are exposed to radiation their activity is retarded later there may be a short period of increased activity before return to normal If the dose is large enough the cells may not recover When a mass of tissue-containing cells of varying sensitivity is exposed to radiation the more sensitive cells may not recover those of medium sensitivity recover to a varying extent and the more resistant cells may show no effect from the exposure The end results are a higher percentage of the more resistant cells in the irradiated area This explains the presence of large amounts of fibrous tissue in these areas and the fact that recovery after injury in irradiated tissue is slow

Cells of the same kind vary within wide limits in their sensitivity depending upon their age and activity at the time of exposure to irradiation Therefore a dose which will produce a given effect cannot be predicted except within a rather wide range The normal tissues of the human body most easily affected by irradiaton are those composed of rapidly growing cells, such as the white blood corpuscles the hair follicles the epithelial cells of the skin the growing epiphyses of bone the blood forming organs and the gonads In abnormal tissue the greatest

sensitivity is evident in those tissues composed of cells approaching the embryonic types and those which are growing rapidly Most tumors are more sensitive than corresponding normal tissue

The curability of a tumor should not be confused with its sensitivity Some radioresistant tumors are curable because of their location and the character of the normal tissue surrounding them The effect of radiation is not entirely due to the size of the dose, but is also influenced by the rate at which it is given and by the time between the beginning and the completion of the treatment When the treatment is interrupted and continued after several days, this effect may become of considerable importance, since the more resistant normal cells may recover completely during the intervals between treatment, while the more sensitive malignant cells do not, the effect on the latter cells being cumulative On the organism as a whole the effect will depend upon the size of the area exposed, its location and the size and intensity of the dose

With the development of large quantities of fissionable materials which emit enormous quantities of radiation similar to that of radium knowledge of the symptoms from and the effect of, irradiation on the body as a whole becomes of increasing importance Reports of the radiation effects on the inhabitants of the cities of Japan on which the first atomic bombs were dropped have already been made by competent medical observers During the experimental bombings at Bikini a considerable number of animals were exposed, and the results of these experiments are becoming available as have the results of similar observations in the laboratory As would be expected the effect of exposure to radiation produced by fissionable matter does not differ from that produced by the roentgen ray, the cathode ray and the rays of radium except in intensity

The symptoms of radiation sickness are anorexia nausea and vomiting followed by diarrhea which may be bloody If the exposure is not severe or prolonged the patient recovers after a varying period of time, with very intense exposure death may occur within a few hours When exposure is fairly severe or prolonged, severe injury to the blood and to the blood forming organs occurs, the white blood cell count falls rapidly, these cells often disappearing from the blood stream within days or weeks Transfusion of whole blood may stay the process but if the blood forming organs have been severely injured death usually follows In general the treatment of radiation sickness is supportive, there is no specific remedy

If the skin is exposed to a sufficient amount of irradiation no matter

what its source, an erythema is produced This erythema is confined to the part exposed and will not spread Its intensity and the time of its appearance may be a matter of hours or weeks depending on the intensity of the exposure and the wave length of the irradiation The erythema is followed by tanning similar to that which is caused by exposure to the rays of the sun Slightly larger doses produce blistering followed by desquamation, with still larger doses complete destruction of the skin third degree burn occurs Lesions of this type induced by x ray the rays of radium or now those produced by fissionable materials are very painful and difficult to heal The chronic ulcers which may develop are prone to the formation of malignant tumors When healing does take place in heavily irradiated tissues, the area is never the same as before exposure It no longer has the vitality of normal tissue it is less resistant to infection or to trauma and following an injury extensive sloughing even of the entire area involved may occur Surgical procedure including such heavily irradiated areas are always hazardous Deep seated organs or tissues which are particularly sensitive to irradiation may be severely damaged although no visible change has taken place in the overlying tissues.

Protection from injury due to irradiation is of more importance to the physician or technician who may be exposed than to the patient in whom exposure is deliberate and necessary The best means of protection is confining of the radiation within the area intended this is accomplished by the use of barriers of lead or of other appropriate material In the case of alpha and beta rays of radium the cathode rays very low voltage x rays and the low energy radiation from fissionable materials considerable protection is afforded by little more than clothing With the use of x rays developed at high potentials and from gamma rays, considerable quantities of heavy metal are necessary to shield the radiation from hazardous spread Certain rays composed of high speed particles without an electrical charge are better absorbed by barriers of low atomic number such as water than they are by materials such as lead There are instances in which an adequate protective barrier cannot be provided for these minimum exposure must then be obtained by two means, (1) by keeping the time of exposure as small as possible and (2) by staying as far away as possible from the source of radiation As the intensity of all radiation varies inversely as the square of the distance this latter is of particular value In the handling of radium and other radio active material speed and a respectful distance are especially

to be recommended It has been accepted that more than 0 2 r* per day is an excessive amount of radiation which may be ultimately detrimental to the well being of those so exposed

The Physical Properties of X-Ray and Radium

X-rays are a part of the electromagnetic spectrum, the same as radio-waves, sunlight and ultraviolet light They are of extremely short wave length, extending in the spectrum from ultraviolet So-called gamma rays are no more than extremely short x-rays and are usually the product of the disintegration of nuclei of radium and other unstable elements The most striking characteristics of x-rays and gamma rays are their ability to penetrate substances which are ordinarily opaque to the rays of greater wave length

For an understanding of the nature and production of x-rays certain elementary facts regarding the structure of matter should be reviewed In so far as is known at the present time the unit of structure of all matter is the atom each being characterized by certain chemical and physical properties, which are determined by the electrical charge the atom carries and by its weight All atoms are in turn composed of certain smaller units, which are always the same, regardless of the nature of the atom they form, they are the electron, the proton and the neutron The smallest of the three is the electron, which carries a negative charge and contributes but little to the mass of the atom it helps to form but does determine to a large extent the chemical characteristics of the element A proton is a larger, positively charged mass A neutron is a unit having mass alone being without any electrical charge, it can be thought of as an electron and proton in combination The two units, the proton and the neutron, form the nucleus or the greater part of the mass of the atom and are responsible for its physical characteristics Other less well known particles need not be discussed here

All the particles in combination make up the atom, which may be thought of as an exceedingly small solar system made up of a central sun the positively charged nucleus composed of protons and neutrons about which are arranged in an orderly fashion the electrons The number of electrons in the outer orbit and the number of mass units in the nucleus are characteristic of each element Each atom is neutrally charged, the number of electrons in the cloud about the nucleus at all

* r = the abbreviation for the international Roentgen — the unit measurement of x rays

times equals the number of protons in the nucleus Hydrogen for example which has an atomic number of 1 has one electron outside and one proton in the nucleus The mass number however is not always the same as the number of protons in the nucleus thus helium, whose atomic number is 2, has an atomic weight of 4 helium therefore must have in addition to the protons in its nucleus neutrons and 2 electrons

Energy is required to impart motion to any object no matter how small and when the motion of this object is arrested or altered a certain amount of that energy is again released When a rapidly accelerated electron is suddenly arrested its energy is released in the form of heat light and a small per cent (0 .5 per cent) in x rays Roentgen rays are produced when matter is bombarded by a stream of negative electrons It is necessary that the electrons have a very high speed and that they are brought to a sudden stop In order to avoid the resistance of air this stream of electrons is produced in a vacuum bulb the x ray tube They originate from a hot metalic filament and are accelerated in an electric field that is, they are produced at the negative pole and move toward the positive pole The higher the voltage on the tube terminal the faster the electrons move and the shorter the wave length of the x ray produced when they are stopped This sudden arrest of the stream of electrons is brought about by placing a metal block the target in the path of the stream The higher the atomic weight of the metal composing the block the sharper will be the arrest of the electrons and the shorter the wave length of the x rays produced In order to focus the stream of electrons on the target a cup like device is placed at the cathode just behind the hot filament producing the electrons The sharper the focus the sharper the image produced by the x rays and the more intense the heat generated at the focal spot Since only 0 per cent of the energy contained in the electron is converted into x ray the remaining 99 8 per cent is dissipated in the form of heat Most x ray tubes are equipped with some arrangement for getting rid of this excess heat

The gamma rays of radium have their origin in the sudden acceleration of electrons which accompanies the disintegration of radio active atoms, they are similar in their physical and biological properties to those of x rays produced at extremely high voltages Radium also ejects two other types of rays during the course of its disintegration which are not a part of the electromagnetic spectrum but are rather streams of small particles, — the alpha rays which are positively charged particles identical with the nucleus of helium and the beta rays which are streams of elec

trons It is for the purpose of removing these undesirable rays that radium applicators ordinarily are encased in heavy metal jackets

Radio active isotopes, which are becoming of increasing importance in medicine, are produced by the bombardment of matter by various subatomic particles travelling at a very high speed with the result that the nuclei become unstable by reason of the addition of one or more of these particles to the nucleus beyond its normal complement or the ejection of one of the particles it already contains, thus producing an unstable relationship between orbit and nucleus Restabilization occurs with the ejection of a particle or quantum of energy at a rate characteristic of each isotope, commonly expressed as its "half life", i e, the time which it takes for activity to be reduced to half

Since certain elements, when introduced into the human body, are deposited in definite organs or tissues (for example, phosphorus is deposited largely in bone) by a selection of the proper element a predetermined amount of irradiation can be given to those organs or tissues by introducing the element into the body after it has been made radio-active It is also possible by this method to determine the final disposition of various substances Much work has been done already along these lines, and many improtant facts have been discovered

It is well to remember that the effect on living tissues is the same whatever the source of the radiation used and that this effect is dependent upon the total dose and the time factors, not upon its source

Principles Governing Use of Radiation in Therapeutics

In considering the use of any therapeutic measure the following questions must be kept constantly in mind (1) Will the procedure cure the patient or relieve his symptoms? (2) Are there other measures which will accomplish the same results with less suffering on the part of the patient or which produce a better end result?

The fact that a cure can be produced by radiation does not always justify its use This is especially true where the dose required to bring about the desired results will cause permanent damage The radiologist must, therefore be familiar not only with the results obtained with the various forms of radiation, but he must also have a working knowledge of other procedures used in the treatment of these diseases The importance of establishing a correct diagnosis before radiation treatment is undertaken cannot be over estimated It is rarely justifiable to exceed the erythema dose before the correct diagnosis has been determined by

biopsy, the only exception being when the lesion is very small or known to be malignant

The use of radiation in therapeutics is based upon the following fundamental principles governing the reaction of living tissues to radiation. With small doses of radiation for every tissue there may be periods simulating increased activity. With larger doses physiological processes are inhibited, and if the exposure be long enough, death ensues. Certain kinds of cells, notably such as are immature or rapidly dividing, are more susceptible to the action of rays than others. When the physician has recognized the nature of the disease, he has, insofar as he understands these principles, a basis for selecting the proper technic for the application of rays.

The following examples of the effect of radiation are of interest. Those handling tubes of radio-active substances without proper protection and caution were early annoyed by irregularities in the growth of their nails. Growth and exfoliation of the epidermis were increased, and the skin took on an appearance of premature senility. Premature senility of growing tissues often follows exposures to rays. The hematopoietic and lymphoid tissues exhibit marked ultimate changes in function under the influence of x rays even in such small doses that no effect is noticed on the *intervening tissues. Sex cells are destroyed with a readiness that* requires extreme precaution to prevent temporary or even permanent sterility.

Cells of many pathological new growths, the regenerating tissues of wounds or injuries, cartilage in the process of ossification, perhaps the growing tissues resulting from bone grafts, and cells of other pathological or rapidly growing conditions are more susceptible than the normal tissues surrounding these regions.

As a general rule, an effort is made to use a dose above that needed to destroy the diseased tissue and yet not great enough to interfere materially with the functions of normal tissues.

The estimation of dose is rather difficult; only a person with long experience in the use of x rays can realize the variations in resistance not only of different types of disease but of different persons having the same disease in an apparently similar form. For the radiation of deep seated organs filters of one kind or another are used to allow the passage of only the more penetrating rays. The filter absorbs the soft rays, i.e., those for which the tissues have a high absorption index. The transmitted rays, because of their lower absorption index, are not so rapidly absorbed near the surface of incidence; the amount of destruction of the

superficial tissues, therefore, is lessened. Combinations of two or more sources of rays often are used with excellent results. For instance in some cases of internal growths the radium tube is inserted into the organ while x-rays are administered through the body-wall, thus exposing the tissues to a thorough cross-fire. Each method of application is useful in its own sphere but must be chosen to suit the case.

Perhaps the most striking and widespread use of radiation is in the treatment of cancer and other tumors. Such growths exhibit varying degrees of susceptibility to this form of treatment from some tumors arising in germinal epithelium and lymphoid structures which quickly melt away before the radiation, to the most resistant form of tumor arising in nerve tissues. In spite of the remarkably gratifying effect produced at times radiotherapy has not reached such a sure stage that it is generally used in preference to surgery, but with improvement in technic and a better knowledge of end results its field is increasing. Where surgical methods are impossible or inadvisable on account of the advanced stages of the disease, radiation may at the very least relieve pain, prevent foul discharge and render the patient comfortable for a time. In these cases it should be remembered that the treatment is palliative and the patient should not be made more uncomfortable, than he already is by heavy dosage in an ill-advised attempt to cure.

The work of Ewing has added greatly to our knowledge of the effect of radiation upon the various forms of neoplastic diseases, his conclusion may be summarized as follows: that the factors entering into radiosensitivity are numerous and sometimes rather obscure, that the general condition of the patient has an important influence on the behavior of the tumor under treatment, that there is a definite relation, not always uniform, between grade of malignancy and radiosensitivity, and that all these matters require careful evaluation before radiation therapy can be intelligently conducted and its results predicted.

The most important factor which renders tumors resistant is the desmoplastic property or tendency to produce growth of connective tissue. This fact is observed most clearly with epidermoid carcinomas and various sarcomas and with most glandular carcinomas while it is absent with lymphomas and most embryonal growths. Even the most cellular anaplastic types of squamous epidermoid carcinomas and of sarcomas retain enough of this primitive function to render their complete sterilization difficult.

Highly vascular tumors melt down rapidly under radiation from necrosis of capillary endothelium often with interstitial hemorrhage and

sometimes with dangerous intoxication, or the slow progress of obliterating blood supply may lead to bulky necrosis and late sloughing

The location or bed of the tumor has much influence on the results of radiation In fat tissue tumor cells find abundant sources of nourishment but are protected from a ready attack by leukocytes and granulation tissue

The lymph nodes enjoy peculiar advantages for the control of tumor cells The distended capsules restrict the circulation and exert pressure on the growth but malignant cells in lymph nodes are more resistant to radiation than when in the primary tumor Lymphocytes and plasma cells have a controlling and even destructive effect on many tumor cells Under some circumstances lymph nodes produce much cellular granulation and connective tissue which incarcerates and destroys tumor cells

Active infection seems to interfere with successful radiation This is particularly true if the dose of necessity is large and may be due to injury to the surrounding normal tissue with a lowering resistance and spread of the infection Heavy treatment generally aggravates the inflammatory process sometimes seriously

When tumor tissue has been radiated with insufficient dosage over a long period of time it acquires a resistance to further irradiation and healing will not take place unless extremely heavy doses are given Cases of this kind especially where they show evidence of damage to the skin are better treated surgically According to Ewing the histological appearance of such irradiated tissue is that of dense fibrous tissue surrounding small groups of malignant cells He believes that this type of tissue protects the cells from further attack and gives it the name abortive fibrosis In general the more malignant and the more rapid growing a tumor is the more sensitive it is to irradiation but there are many other factors which enter into clinical malignancy and this statement cannot be applied to all cases There are many exceptions not all malignant medullary tumors are sensitive A striking example is melanosarcoma which is generally both medullary and resistant A distinction should be made between sensitivity and curability Although many highly malignant medullary tumors disappear rapidly under irradiation it not infrequently happens that remnants remain to reoccur later or the patient may die from distant metastases An understanding of these facts is of the greatest importance in the selection of the form of therapy in a given case Very malignant rapidly growing tumors usually are the group in which surgery fails but these tumors are as a rule especially sensitive to radiation and the local lesion should be cured by this method On the other hand

some tumors of low sensitivity, because of their location, can be safely destroyed with large doses

The proper grading of tumors according to their malignancy and radiosensitiveness is of the greatest importance to the radiotherapist and to the surgeon, considerable progress along this line has been made already by Ewing and others The combined use of surgery and irradiation has not resulted in the degree of success which would naturally be expected The removal by surgical means of tumor remnants after irradiation usually results in a rapid spread of the disease Post-operative radiation to destroy any remaining malignant tissue has not definitely raised the percentage of cures This is probably due to the fact that the treatment given is not of sufficient intensity to destroy the tumor cells, naturally one hesitates to give a dose large enough to injure normal tissue unless there is certainty that such cells are present Prolonged post operative treatment is probably of no value and should be abandoned The successful treatment of malignant disease, either by irradiation or surgery will depend largely upon a knowledge of the pathology and life history of tumors, their response to irradiation or surgery and upon the degree of cooperation between the radiotherapist, surgeon and internist

While it is generally true that the results are largely dependent upon the total dose regardless of the quality of radiation used or the duration of exposure reports from the Curie Institute in Paris and the St Bartholomew s Hospital in London seem to show that slow growing tumors are less able to recover from relatively small doses of radiation than is the surrounding normal tissue When small daily doses are given over a long period of time the effect on the diseased tissue is considerably greater than upon the surrounding normal tissue A modification of this technic has been developed by Coutard in which special attention is given to the size and spacing of the dose

An excellent review of our knowledge of the effect of radiation either with x-ray or radium upon animal and vegetable life including the normal tissue of the body is found in the works of Colwell and Russ and in a more recent publication by Pack and Livingston In general it may be stated that all forms of life can be destroyed by irradiation but that the bacteria and animal parasites with which man may be afflicted are more resistant to radiation than are the normal tissues of the body, and that doses large enough to destroy them will result in severe and lasting injury prohibiting their use that young animals are particularly sensitive to radiation and that exposure to even moderate dosage may result in retardation or abnormality of growth This fact is of importance to the

radiotherapist in his treatment of children Exposures which fail to produce injury to the skin may result in retardation or abnormality of growth of underlying organs

The internist and practitioner in medicine should have a knowledge of the dosage used in x ray and radium and the factors which enter into the estimation of such dosage This is necessary not only in the field of therapy but also in that of diagnosis The use of the fluoroscope in medical diagnosis is becoming more and more general and it is not unusual for the physician practicing one of the medical specialties to have such an instrument in his office for his own personal use It is probably unwise for one to undertake this work until he has a working knowledge of the factors on which x ray dosage depends and of the methods of protection The absence of such knowledge as this was a direct factor in the production of the injuries received by the early workers in this field When the x ray is used as a diagnostic procedure the usual method of estimating the dose received by the patient and operator is the so-called mathematical method By this method the dose is estimated from the following data the distance of the part from the source of light that is the focal spot of the x-ray tube the duration of the exposure the milliamperage passing through the tube during the exposure the voltage upon the tube terminal at the time the exposure is made and the character and kind of filtration used

Perhaps the most important factors and the one most likely to be neglected are distance and filtration The effect diminishes with the square of the distance In other words, if the distance is doubled the effect is reduced to one fourth Filters of varying thickness are used to shut out the longer wave length those which are absorbed in the skin and subcutaneous tissue, thereby reducing the exposure to that which is absolutely necessary and diminishing the chances of an undesirable skin reaction The purchaser of roentgen apparatus or of radium should know the dose required to produce an erythema with this apparatus and should never exceed it The dosage in x ray therapy is expressed in skin units, s u erythema dose or r units the latter is now in general use and probably should be used exclusively It is the unit of dosage accepted by the International Congress of Radiology at Stockholm in 19 8 and is defined as that quality of x radiation which when the secondary electrons are fully utilized and the wall effect of the chamber is avoided produces in one cubic centimeter of atmospheric air at 0 centigrade and 76 cm of mercury pressure such a degree of conductivity that one electrostatic unit of charge is measured at saturation current This unit of

x-ray dose is called "the roentgen" and is designated by the small letter "r" The intensity is measured in r units per second Satisfactory instruments are now available for the measurements of x-radiation directly in r units (Fig 1) The number of r units required to produce an erythema on the human skin varies considerably with the voltage and filtration used with 200 K V and 0 5 mm copper filter, the dose is about 800 r,

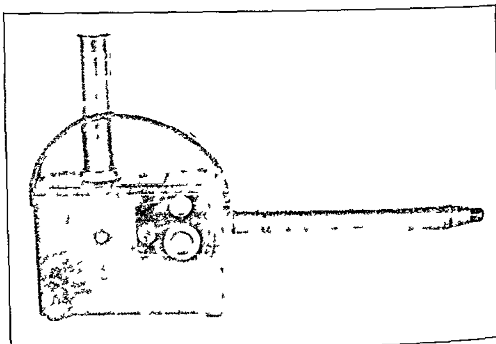


Fig 1 The Victoreen r meter consists of a small ionization chamber rigidly connected to a string electrometer the scale of which is calibrated in international units A flashlight battery and switch are included in the electrometer for illuminating the scale The electrometer is charged by a small built in static charger The electrometer is 6 x 4 x 2 5 inches The chamber tube is 7 inches long With the carrying case the total weight is 10 pounds

The instrument is placed in any position but with the chamber at the point where it is desired to measure intensity The chamber is exposed for one minute to the rays and the scale read the figure read being the r per minute Where very small intensities are to be measured the chamber may be exposed five minutes instead of one minute and the number of units divided by five The reverse applies to the measurement of high intensities

with lower voltages and less filtration the erythema time is shortened so that with the kind of radiation used in superficial therapy the dose is about 250 r In the therapeutic use of radium the dose is expressed in milligram hours for the elements and in millicurie hours for the emanation These figures are obtained by multiplying the number of milligrams or millicuries in the applicator used by the time in hours To obtain the dose actually received by the skin it is necessary to take into considera

tion the distance and filtration used The radiotherapist is also equipped with anatomical charts and absorption curves (see Table I) with which it is possible for him to estimate quite accurately the dose received at the depth In estimating the dosage to be used in a given case we must consider not only the sensitiveness of the lesion to be treated but also the skin tolerance dose and the dose which vital organs in the path of the beam may receive

TABLE I — RELATIVE INTENSITY MEASUREMENTS

(200 kv 4 ma 0 5 mm Cu + 2 mm Al 50 cm S T D)

Cm Depth Water	20 cm Diam Per cent	16 cm Diam Per cent	14 cm Diam Per cent	10 x 8 cm Per cent	8 x 6 cm Per cent	5 cm Diam Per cent
0	100 0	100 0	100 0	100 0	00 0	100 0
1	100 0	100 0	99 0	9 0	96 5	95 0
2	95 0	94 0	91 0	91 5	89 0	84 0
3	86 0	84 5	84 0	82 0	7 0	3 0
4	78 0	6 0	5 0	3 0	68 0	62 0
5	72 5	69 0	6 0	64 5	58 5	53 5
6	64 0	61 5	60 0	56 5	52 0	46 0
7	56	54 5	53 0	48	43 0	38 0
8	49 0	47 0	46 0	42 0	35 0	31 5
9	43 0	40 0	39 0	36 0	29 0	26 5
10	38 0	3 5	34 0	30 0	2 0	2 5
11	33 5	29 5	28	2 5	22 0	18 0
12	28 5	27 0	2 0	2 0	18 0	15 5
13	26 0	24 0	22 0	18 0	16 0	13 0
14	22 0	21 0	18 0	1 0	13 5	10 5
15	17 5	17 0	15 0	13 0	11 0	8 0
16	16 5	15 0	13 0	11 5	8 5	7 5
17	14 0	13 0	11 5	9 5	5	5 5
19	10 0	8 5	8 0	0	4 5	3 5

(From Weatherwax) This table shows the intensity of radiation of various depths below the surface when the so-called high voltage x rays are used using the various size field

Where large doses of short wave x ray or heavily filtered radium are given it is customary to prolong the treatment over a considerable period of time This is done to avoid roentgen sickness or to make the dose to the malignant tissue more effective These doses usually are given in daily sittings and often require from one to two weeks the total dosage may be double that which could be given at a single sitting (see Table II) When the patient is undergoing this form of treatment it is desirable but not absolutely necessary that he be hospitalized The internist should realize that proper radiation treatment often requires the production of

x-ray dose is called "the roentgen" and is designated by the small letter r' The intensity is measured in r units per second Satisfactory instruments are now available for the measurements of x-radiation directly in r units (Fig 1) The number of r units required to produce an erythema on the human skin varies considerably with the voltage and filtration used, with 200 K V and 0 5 mm copper filter, the dose is about 800 r,

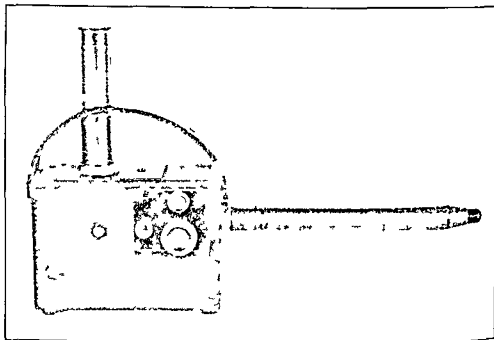


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operations are necessary. This form of treatment should be reserved for those cases where there is a possibility of cure by completely destroying the local process. Once metastasis has taken place, and the disease has become general, such massive doses are rarely justifiable, also they are seldom if ever used in non-malignant conditions. The production of a well-marked erythema usually results in some permanent damage to the skin and is followed by telangiectasis and skin atrophy. When heavy treatment is given over certain parts of the body there is some danger of injury to the internal organs. For example, radiation over the throat may result in injury to the larynx with resulting edema and extreme difficulty in breathing. Treatment over the abdomen may result in injury to the intestinal mucosa followed by diarrhea, sometimes bloody, and in extreme cases by anemia and rapid loss of weight. In some of these cases the result has been fatal.

With even moderate doses over the thorax or abdomen, particularly when the liver is included, constitutional symptoms of varying severity may result, the so-called radiation sickness; such symptoms may occur with radiation from x-ray or radium. This phenomenon was observed by the early users of x-ray for therapeutic purposes and has received a large amount of attention and study, but its exact cause still is unknown. In general it may be stated that there are three distinct forms, probably due to as many causes: first, psychic; second, toxic, and third, indirect or unknown. The first occurs only in patients who have been made sick previously by the treatment and is influenced to a considerable extent by surroundings, particularly the odors from high-tension discharges. Changing to another clinic or the removal of all odors sometimes will prevent a recurrence of these symptoms. Toxic sickness results from the rapid breaking down of large tumor masses; its symptoms and treatment do not differ from that of similar toxic conditions. The third form of sickness is the most difficult to handle, since its cause is unknown and no specific treatment can be planned. Its appearance seems to depend on the size and location of the area exposed, the rapidity with which the dose is given and the general condition of the patient. A patient whose intake has been low from any cause, those who are dehydrated and debilitated, seem to be especially susceptible. For this reason it is desirable not to attempt radiation too soon after major operations or in patients whose food intake has been limited for some time, but to wait until the patient is taking an adequate amount of food and liquids before starting the treatment. With a large field over the abdomen or lower thorax the daily dose should be small and the treatment prolonged. When the sickness

an erythema of the skin which may result in some cases in permanent damage This is particularly true in the treatment of malignant disease where inadequate dosage may be worse than useless When there is a possibility of cure by increasing the dose, it is justifiable to destroy considerable normal tissue which usually can be repaired later surgically The fact that internists and patients do not understand the necessity for

TABLE II — SATURATION LOSS IN PER CENT FOR ONE TO SEVEN DAYS WITH VARYING INITIAL INTENSITIES

(200 kv 0.5 mm Cu + 2 mm Al Filter)

Per cent	Loss						
	1 Day	Days	3 Days	4 Days	5 Days	6 Day	7 Days
5	0.3	0.5	0.8	1.0	1.2	1.4	1.6
10	0.5	1.0	1.5	2.0	2.4	2.8	3.2
15	0.8	1.6	2.3	3.0	3.6	4.2	4.8
20	1.1	2.1	3.0	3.9	4.8	5.6	6.4
25	1.3	2.6	3.8	4.9	6.0	[illegible].0	8.0
30	1.6	3.1	4.6	5.9	7.2	8.4	9.6
35	1.9	3.6	5.3	6.9	8.4	9.8	11.2
40	1	4.2	6.1	9	9.6	11.2	12.8
45	4	4.[illegible]	6.8	8.9	10.8	12.6	14.4
50	2.6	5.2	7.6	9.0	12.0	14.1	16.0
55	2.9	5.7	8.4	10.8	13.2	15.5	17.6
60	3	6.2	9.1	11.8	14.4	16.9	19.2
65	3.4	6.8	9.9	12.8	15.6	18.3	20.8
70	3.7	7.3	10.6	13.8	16.8	19.7	22.4
75	4.5	[illegible].8	11.4	14.8	18.0	21.1	24.0
80	4.2	8.3	12.2	15.8	19.2	22.5	25.6
85	4	8.8	12.9	16.8	20.4	23.9	27.2
90	4.8	9.4	13	[illegible]	21.6	25.3	28.8
95	5.0	9.9	14.4	18	22.8	26.7	30.4
100	5.3	10.4	15.2	19.[illegible]	24.0	28.1	32.0

(From Weatherwax) In column one the dose is indicated in percentages of the tolerance dose under the heading Loss the percentage of energy lost per day is indicated that is with a 100 dose about *two thirds remain at the end of seven days*

this kind of treatment has resulted in frequent malpractice suits and is one of the factors which has prevented the proper development of this form of treatment The degree of permanent damage depends not only upon the size of the dose but upon the location and size of the area treated Very large doses may be given to areas of one centimeter or less in diameter, and the resulting ulcer usually will heal completely In larger areas however, complete healing rarely takes place and plastic

b An operator should place himself as remotely as practicable from the x ray tube It should not be possible for a well-rested eye of normal acuity to detect in the dark appreciable fluorescence of a screen placed in the permanent position of the operator

c The x ray tube should be surrounded as completely as possible with protective material of adequate lead equivalent

d The following lead equivalents are recommended as adequate

X rays Generated by Peak Voltage	*Minimum Equivalent Thickness of Lead*
Not Exceeding	mm
75 kV	1 0
100 kV	1 5
125 kV	2 0
150 kV	2 5
175 kV	3 0
200 kV	4 0
250 kV	5 0

e In the case of diagnostic work the operator should be afforded protection from scattered rays by a screen of a minimum lead equivalent of 2 mm

f In the case of x ray treatment the operator should be stationed completely outside the x ray room behind a protective wall of a minimum lead equivalent of 2 mm This figure should be correspondingly increased if the protective value of the x ray tube inclosure falls short of the values given in paragraph 3 (*d*) In such event the remaining walls, floor and ceiling may also be required to provide supplementary protection for adjacent occupants to an extent depending on the circumstances When supervoltage x rays or large amounts of radium are used the protection from the direct rays should have the equivalent of six inches of lead and from scattered rays the equivalent of one half inch of lead

g Screening examinations should be conducted as rapidly as possible with minimum intensities and apertures

h The lead glass of fluorescent screens should have the protective values recommended in paragraph 3 (*d*)

i In the case of screening stands should not be used

develops, rest with attention to the elimination of the waste products of the body and in some cases the intravenous injection of glucose or the giving of large doses of vitamin B1 has been helpful

The effect of radiation is cumulative When a dose has been given which approaches that which will produce an erythema on the exposed skin surfaces it should not be repeated over the same area for a period of at least one month In prolonged treatment with high voltage x-rays or heavily filtered radium the lapse period should be longer, probably two months at least

Various radiological societies have adopted recommendations governing the use of x-rays and radium for the protection of operators and patients At the International Congress of Radiologists held in Stockholm in 1928 a committee to standardize these regulations was formed this committee has drawn up a set of rules which have been accepted by the international society and published in the various x-ray and radium journals throughout the world The following is an abstract of these rules and regulations

1 Working hours etc for those actually exposed to the rays
   - *a* Not more than seven working hours a day
   - *b* Not more than five working days a week The off days to be spent as much as possible out of doors

2 General x-ray recommendations
   - *a* X-ray departments should not be situated below ground floor level
   - *b* All rooms including dark rooms should be provided with windows affording good natural lighting and ready facilities for admitting sunshine and fresh air whenever possible
   - *c* All rooms should be provided with adequate ventilation
   - *d* All rooms should preferably be decorated in light colors
   - *e* X-ray rooms should be large enough to permit a convenient lay out of the equipment A minimum floor area of 250 square feet (25 square meters) is recommended for x-ray rooms and 100 square feet (10 square meters) for dark rooms
   - *f* A working temperature of about 18° C (65° F) is desirable in x-ray rooms

3 X-ray protective recommendations
   - *a* An x-ray operator should on no account expose himself unnecessarily to a direct beam of x-rays

b An operator should place himself as remotely as practicable from the x ray tube. It should not be possible for a well-rested eye of normal acuity to detect in the dark appreciable fluorescence of a screen placed in the permanent position of the operator.

c The x ray tube should be surrounded as completely as possible with protective material of adequate lead equivalent.

d The following lead equivalents are recommended as adequate:

X rays Generated by Peak Voltage Not Exceeding	*Minimum Equivalent Thickness of Lead* mm
75 kV	1.0
100 kV	1.5
125 kV	[illegible]
150 kV	[illegible]
175 kV	3.0
200 kV	4.0
225 kV	5.0

e In the case of diagnostic work the operator should be afforded protection from scattered rays by a screen of a minimum lead equivalent of [illegible] mm.

f In the case of x-ray treatment the operator should be stationed completely outside the x ray room behind a protective wall of a minimum lead equivalent of [illegible] mm. This figure should be correspondingly increased if the protective value of the x ray tube inclosure falls short of the values given in paragraph 3 (*d*). In such event the remaining walls, floor and ceiling may also be required to provide supplementary protection for adjacent occupants to an extent depending on the circumstances. When supervoltage x rays or large amounts of radium are used the protection from the direct rays should have the equivalent of six inches of lead and from scattered rays the equivalent of one half inch of lead.

g Screening examinations should be conducted as rapidly as possible with minimum intensities and apertures.

h The lead glass of fluorescent screens should have the protective values recommended in paragraph 3 (*d*).

i In the case of screening stands should not be used

j Screening should provide adequate arrangements for tables protecting the operator against scattered radiation from the patient

k Inspection windows in screens and walls should have protective lead values equivalent to that of the surrounding screen or wall

l Efficient safeguards should be adopted to avoid the omission of metal filter in all x-ray work

m Protective gloves, which should be suitably lined with fabric or other material should have a protective value not less than ½ mm lead throughout both back and front (including fingers and wrist) Protective aprons should have a minimum lead value of ½ mm

3 Electrical precautions in x-ray rooms

a All equipment should be of the shock-proof variety and unless there are reasons to the contrary, metal parts of the apparatus should be efficiently grounded Modern x-ray equipment is so constructed that the patient and operator are almost completely protected from electrical shock and from all except the direct x-ray beam They are not protected from scattering from the walls of the room, and the operator is exposed to scattering from the patient It should not be forgotten that there is no protection from the direct beam In fact modern equipment because the danger of shock has been eliminated allowing the distance between the source of the ray and the parts exposed to be shortened is much more dangerous from this source than the older apparatus

d A separate room should be provided for the 'make up' of screened radium tubes and applicators, and this room should be occupied only during such work

e In order to protect the body from the penetrating gamma rays during handling of the radium, a screen of not less than one inch thickness of lead should be used, and proximity to the radium should occur only during actual work and for as short a time as possible

f The measurement room should be a separate room and it should contain the radium only during its actual measurement

g Nurses and attendants should not remain in the same room as patients undergoing radium treatment

h All unskilled work or work which can be learned in a short period of time should preferably be carried out by temporary workers who should be engaged on such work for periods not exceeding six months This applies especially to nurses and those engaged in make up applicators

i Discretion should be exercised in transmitting radium salts by mail In the case of small quantities it is recommended that the container should be lined throughout with lead not less than 3 mm thick It is more satisfactory to transport large quantities by hand in a suitably designed carrying case

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CHAPTER VIII

CALORIMETRIC METHODS OF STUDY OF DISEASE

By Eugene F. Du Bois

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HISTORY OF CALORIMETRY

In the first two decades of this century the term calorimetry was used only in connection with the bomb calorimeters or large respiration chambers which measure heat by the method of direct calorimetry. Recently it has been applied to the work of the small types of respiration apparatus which measure heat production by the indirect method. This change is due to the fact that the older and more complicated respiration calorimeters are being abandoned in favor of the smaller and simpler machines.

It is difficult if not impossible to understand the methods of indirect calorimetry unless one grasps the principles of direct calorimetry which are based on fairly simple physical methods of measurement. When a man is placed in the chamber of a respiration calorimeter, he is treated as a physical object producing and eliminating a certain amount of heat. Under average conditions about 25 per cent of this is lost in vaporization, about 15 per cent in conduction and convection and the remaining 60 per cent in radiation. The only way a man can produce this warmth is by the oxidation of foodstuffs. The method of indirect calorimetry estimates by chemical methods the total amount of this oxidation.

The history of clinical calorimetry[1] is one of slow development and gradual adaptation. There is a striking similarity between the calorimeter which measures the oxidation of food in a sick man and the one which

determines the heating value of a sample of food or coal The industrial chemist weighs out a portion of the material to be tested, places it in a strong steel cylinder with a large excess of oxygen and ignites it by



FIG 1 — Bed calorimeter of the Nutrition Laboratory Boston.

means of a glowing platinum wire The heat given off is measured by noting the rise in temperature of the water which surrounds the cylinder

Some of the early calorimeters in which animals and men were studied, consisted of chambers surrounded by water jackets Knowing the weight of the water and the number of degrees rise in temperature it was possible to measure the heat given off from the body To this was added the heat lost in vaporization of water from the skin and lungs Arrangements were made to ventilate the chamber and either prevent or correct for loss of heat in the air A simple apparatus of this type was used by Isaac Ott of Philadelphia in 189- in the study of a man with malarial fever Ten years later Likatscheff and Avroroff of St Petersburgh made similar studies, using the famous calorimeter of Paschutin

Their results are impaired by the fact that they did not appreciate the importance of keeping their subjects absolutely quiet. It was about 1908 that it was first realized that uncontrolled activity of the subject in the

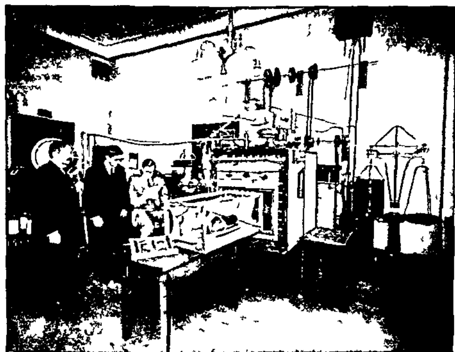


FIG. 2 — This figure shows a small respiration calorimeter built by H. B. Williams for the Physiological Laboratory, Cornell Medical College, New York City. A dog wearing a bandage which holds a rectal thermometer in place is shown lying on a cot suspended from a frame which may be slid into the open chamber of the calorimeter. This accomplished, the front is then sealed. The animal respires within the chamber, the water and carbonic acid which he eliminates are removed by circulating the air through absorbing chemicals, and fresh oxygen is admitted automatically to replace the oxygen absorbed by the animal. The heat produced by the dog is removed by a current of water flowing through a system of pipes within the calorimeter.

respiration chamber caused so large an error that the figures obtained could not be used for purposes of comparison.

The foundations of the modern science of nutrition were built by the experiments on animals and normal men made in the respiration chamber of Pettenkofer and Voit, the respiration calorimeter of Atwater and Benedict, and the dog calorimeters of Rubner and Lusk. Much help was given by the simpler types of respiration apparatus used by Zuntz. During

Magnus Levy, Benedict and others These are fully described by Carpenter[3], who compares the various designs Some consist of spirometers or gas meters into which the patient breathes through a mouthpiece or mask for periods of ten to twenty minutes Others resemble the ventilating system of a calorimeter and the patient either lies in a closed chamber or is connected with the apparatus by means of a mask or mouthpiece The heat production is calculated from the oxygen consumption

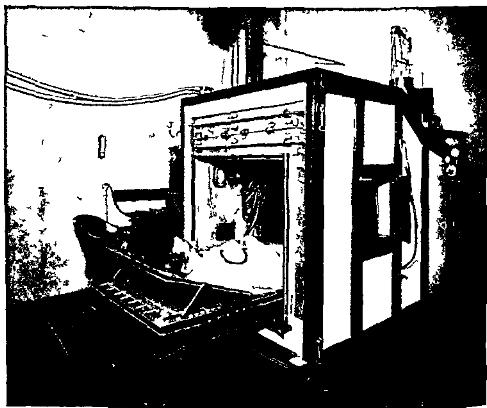


Fig 3 — Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital.

by the method of indirect calorimetry No large clinical study was attempted with calorimeters until 1908, when Benedict and Joslin[15] in Boston began a very extensive series of experiments with diabetics using the small Benedict apparatus and the Atwater-Rosa-Benedict respiration calorimeter The work was done at Boston in the Nutrition Laboratory of the Carnegie Institution of Washington a splendidly equipped plant where extensive investigations had already been made in the metabolism

of normal subjects In this same laboratory Carpenter and Murlin[6] studied the metabolism of pregnant women and for the first time compared in clinical cases the methods of direct and indirect calorimetry

Working in Lusk s laboratory and using the small calorimeter which was built for dogs Howland in 1911 established the fact that the methods

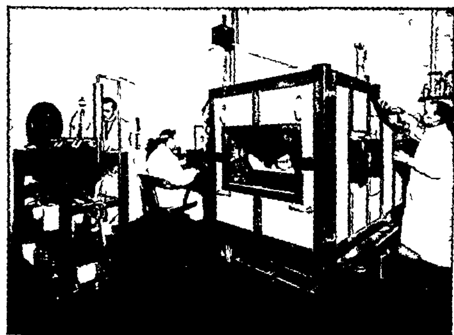


FIG 4 — Sage calorimeter The patient has disobeyed the order to remain quiet and has turned to look at the camera The observer at the left is taking a sample of the air in the box The man seated at the table is reading the electrical thermometers The man at the right is adjusting the device for admitting oxygen

of direct and indirect calorimetry agree closely in the case of infants Under Lusk s direction two years later work with a larger respiration calorimeter was begun by the Russell Sage Institute of Pathology [illegible] in a small room adjoining the medical wards of the Second Medical (Cornell Division of Bellevue Hospital in New York This apparatus was constructed solely for the purpose of clinical calorimetry The patients studied were kept in a specially organized metabolism ward where all food was weighed and all excreta saved for analysis A number of diseases were thus studied in detail under ideal conditions

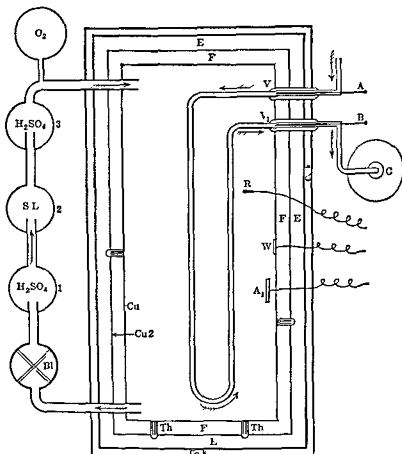


FIG 5 — Schematic diagram of Atwater Rosa Benedict respiration calorimeter

Ventilating System
- *O* Oxygen introduced as consumed by subject
- *3* H_2SO_4 to catch moisture given off by soda lime
- Soda lime to remove CO
- *1* H SO to remove moisture given off by patient
- *Bl* Blower to keep air in circulation

Indirect Calorimetry
- Increase in weight of H_2SO_4 (1) = water elimination of subject
- Increase in weight of soda lime (2) + increase in weight of H SO (3) = CO elimination
- Decrease in weight of oxygen tank = oxygen consumption of subject

Heat Absorbing System
- *A* Thermometer to record temperature of ingoing water
- *B* Thermometer to record temperature of outgoing water
- *L* Vacuum Jacket
- *C* Tank for weighing water which has passed through calorimeter each hour
- *W* Thermometer for measuring temperature of wall
- A_1 Thermometer for measuring temperature of the air
- *R* Rectal thermometer for measuring temperature of subject

Direct Calorimetry
Average different of *A* and *B* × liters of water + (gm water vaporized × 0 586) ± (change in temperature of wall × hydrothermal equivalent of box) ± (change of temperature of body × hydrothermal equivalent of body) = total calories produced

Th thermocouple *Cu* inner copper wall Cu_2 outer copper wall *E F* dead air spaces

Direct Calorimetry

Since practically all clinical calorimetry has been performed in Atwater Rosa Benedict respiration calorimeters, it may be well to describe this instrument briefly. The reader who is interested in the details of the technic and calculation is referred to Lusk's "Science of Nutrition." [illegible] The calorimeter is a closed circuit absolutely shut off from the surrounding atmosphere. Everything eliminated by the subject is caught and measured. This is shown schematically in Fig. 5. The protecting wall is lined with cork. Next to this comes the outer copper wall separated by an air space from the inner copper wall. By means of electrical thermometers, thermocouples, heating wires and cooling coils, the outer copper wall is maintained at exactly the same temperature as the inner wall. Therefore there is no tendency for heat to travel from one wall to the other. In a similar fashion the air which enters the calorimeter is brought to exactly the same temperature as the air which leaves the box. All the heat of radiation and conduction is removed by means of a stream of water flowing at constant rate through pipes at the top of the chamber. The temperature of the water is measured as it enters and as it leaves the calorimeter and the total water for each experimental period is caught and weighed. If the weight of the water in kilograms is multiplied by the average rise in temperature, the resulting figure gives the calories of radiation and convection. The calories lost in the vaporization of water are determined by multiplying the grams of water given off by the patient by the figure 0.584, which represents the heat rendered latent by the vaporization of one gram of water at a temperature of [illegible] C. The rectal temperature of the patient is measured by an electrical thermometer and the amount of heat stored in or lost from the body is calculated from the body weight and specific heat. Thus the total heat production can be determined by the purely physical methods of direct calorimetry.

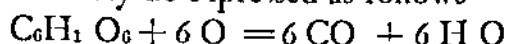
The air in the chamber is used over and over again but is kept pure by circulation through a system of absorber bottles. A powerful blower draws the air from the foot of the box, drives it through the absorbers and then returns a mixture of dry oxygen and nitrogen to the head of the box. The first absorber contains concentrated sulphuric acid and removes all water vapor, the next contains soda lime which removes all carbon dioxid, the third contains sulphuric acid to catch the moisture from the damp soda lime. These are all weighed before and after each period, the gain in weight of the first absorber giving the water of vaporization, the

combined gain in weight of the soda lime and the last sulphuric acid bottle giving the carbon dioxid.

Meanwhile the subject has been absorbing oxygen from the air causing a shrinkage of volume of the contents of the calorimeter. This is compensated by the automatic device which admits oxygen from a weighed steel flask exactly as it is consumed. By weighing this flask again at the end of the period it is possible to determine with nicety the oxygen consumption of the subject. The principles of the technic are fairly simple but in practice it is necessary to make a number of corrections for changes in temperature, barometer, residual air in the calorimeter, heat lost or gained from objects in the calorimeter, etc.

Indirect Calorimetry

A man's heat production may be calculated by the chemical method of indirect calorimetry if the amount of oxygen absorbed, the carbon dioxid eliminated by the lungs and the nitrogen in the urine during a definite period, is known. When a chemical substance, such as starch, is oxidized the process may be expressed as follows:



$$C_6H_{12}O_6 + 6\,O_2 = 6\,CO_2 + 6\,H_2O$$

Carbohydrates, as their name indicates, contain just enough oxygen to combine with the hydrogen in the molecule and form water. This means that the volume of the oxygen absorbed in the above reaction will equal the volume of carbon dioxid produced. In other words, the respiratory quotient $\frac{CO_2}{O_2} = 1.00$. Fat and protein do not contain enough oxygen to combine with the hydrogen in their molecules, so they must absorb some of this gas to form water in addition to that required to produce carbon dioxid. Since fat and protein have fairly definite compositions it is possible to calculate the oxygen absorbed and carbon dioxid produced when a gram of each substance is oxidized, thus obtaining the respiratory quotient, and when these substances are burned in a bomb calorimeter the heat of combustion is obtained. By simple mathematics it may then be ascertained how much heat must be liberated when a liter of oxygen is used in the oxidation of fat or protein or starch (Table I).

For each 100 grams of meat protein oxidized 16.28 grams of nitrogen will appear in the urine. This fact enables us to calculate how much protein has been metabolized in an experimental period and to determine

the grams of oxygen (grams N × 8 45) absorbed and the carbon dioxid (grams N × 9 35) produced in the process *Subtracting these figures* from the totals there remain the carbon dioxid and oxygen of carbohydrate and fat If the respiratory quotient $\frac{CO}{O}$ of this residuum be 1 00 carbohydrate is being oxidized if the respiratory quotient be 0 707 fat is indicated Except in rare instances the figure for the non protein

TABLE I

OXIDATION OF FOODSTUFFS

1 Gram Substance	O_2 Absorbed cc	CO_2 Formed cc	R Q	Calorie	Calories Computed from	
					1 Liter O_2	1 Liter CO_2
Protein	966 3	3 9	0 801	4 316	4 485	5 579
Fat	2 019 3	1 427 3	0 707	9 461	4 686	6 6 9
Starch	828 8	828 8	1 000	4 182	5 047	5 047

quotient is between these points and it is possible to estimate the ratio between the two Thus the actual grams of fat and carbohydrate metabolized during the experiment can be calculated

CLINICAL APPLICATION OF CALORIMETRIC OBSERVATIONS

The importance of this method of study is obvious to the clinician A diabetic can be given an experimental meal and the amount of carbohydrate oxidized each hour determined In the same manner tissue metabolism in various diseases and conditions may be studied The respiration apparatus might be termed a metabolic x ray for examining functions rather than structures

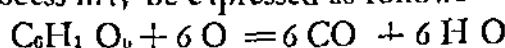
The calorimeter has introduced a new method of determining the average changes in body temperature With a carefully tested instrument the methods of direct and indirect calorimetry agree closely Therefore a man s heat production by the indirect method and his heat elimination by the direct method can be determined The difference between these represents the amount of heat stored in or lost from the body Knowing the body weight and approximate specific heat it is

combined gain in weight of the soda lime and the last sulphuric acid bottle giving the carbon dioxid

Meanwhile the subject has been absorbing oxygen from the air causing a shrinkage of volume of the contents of the calorimeter This is compensated by the automatic device which admits oxygen from a weighed steel flask exactly as it is consumed By weighing this flask again at the end of the period it is possible to determine with nicety the oxygen consumption of the subject The principles of the technic are fairly simple but in practice it is necessary to make a number of corrections for changes in temperature barometer residual air in the calorimeter heat lost or gained from objects in the calorimeter, etc

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period the patient shivered violently and his heat production which had been at the level of 86 calories an hour rose to [illegible]0 calories In forty minutes he stored about 100 calories within his body After the chill his temperature continued to rise, but the rectal temperature rose more rapidly than the average body temperature During the period of high but level rectal temperature the average for the body was still rising Although the heat production had shown a sharp rise during the chill and a drop immediately afterwards there was practically no change in the rate of heat elimination Other experiments have shown the same phenomenon and have proved that the rise of temperature in malaria is due almost entirely to an increased heat production The fall in temperature is due chiefly to a marked increase in heat elimination and especially vaporization The heat production returns almost to normal soon after the chill

The disturbance in the balance between heat production and heat loss with chills is used as an example of maximal effects The results however, can be matched by severe exercise with a rise of internal body temperature to 38 to 39 C (100 to 10[illegible] F) because heat loss does not keep up with heat production until a steady state has been attained In the majority of cases of fever the temperature rises without a chill due to either an increased heat production or decreased heat loss It must be remembered that skin temperature and internal temperature are not always changing at the same rate or even in the same direction For example, the skin usually cools as more and more heat is given off on account of increased sweating or convection

In the last fifteen years there have been many studies of the details of heat loss from human subjects by Winslow Herrington and Gagge Bazett Burton Hardy and DuBois and Army and Navy research groups interested in problems of clothing for extremes of heat and cold[9] [illegible] Not only have there been great advances in the science of clothing but many important facts have been discovered about the skin temperature and the peripheral circulation Physiologists and clinicians are thinking in terms of temperature gradients in different parts of the body In cold environments there are large cool areas near the surface along the veins of the extremities and even along the arteries that are close to the veins Clinicians have appreciated the fact that in shock heating the skin draws a great deal of blood to the peripheral circulation while cooling the skin drives it to the interior of the body

More and more attention is paid to the regulation of heat loss by the insensible perspiration and the emergency mechanism of sweating The

easy to calculate the rise and fall of the average body temperature Experiments in malarial and other fevers have shown that the rectal temperature does not always represent the average changes throughout the

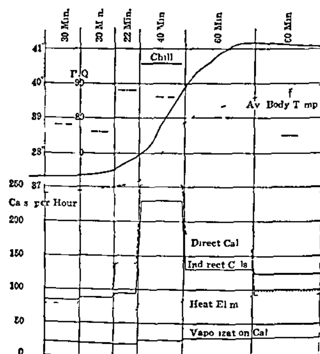


FIG 6 — CHANGES IN METABOLISM CAUSED BY MALARIAL CHILL

The curves show the relationship of heat production and heat elimination before during and after a malarial chill The uppermost line shows the changes in rectal temperature The accompanying dash line shows the changes in the average body temperature The middle dash line represents the heat production in calories as measured by the direct method the solid line the heat production by the indirect method the dotted line the heat eliminated and the lowest solid line the calories lost in the vaporization of water The respiratory quotients are represented above the rectal temperature by dashes for each period

body Every clinician has at times noticed that with a rising rectal temperature, there may be a distinct cooling of the feet and hands A man who weighs 70 kilograms has a surface area of about 1 8 square meters and 15 kilograms of tissue lies within 1 cm of the surface The temperature of this surface layer is intermediate between that of the deeper structures and the surrounding atmosphere Also, the conduction of heat through this layer is variable depending on the blood flow In a patient with malaria (Fig 6) two thirty-minute periods were studied before there was any significant rise in temperature In the third period a distinct rise gave warning of the approaching paroxysm In the fourth

calorimetry agree closely in pathological cases There has been a tendency for investigators to make rather wild speculations when the results of respiration experiments with patients do not seem to follow the laws established with animals and normal men They assume abnormal

TABLE III

GROUPS OF SUBJECTS STUDIED IN THE SAGE CALORIMETER
Comparison of Direct and Indirect Methods

Clinical Calorimetry Paper No	Group	Indirect Calorimetry	Direct Calorimetry	Divergence of Direct from Indirect Calorimetry
		Calories	Calories	Per Cent.
4	7 normal men	4 577 4	4 569 4	−0 2
11	4 normal men	1 634 3	1 670 2	+2 2
15	2 normal men and 1 woman	1 103	1 087 5	−1 5
22	6 normal men	878 8	929 1	+5
12	8 boys 12 to 13 years old	985 9	986 3	+0 0
2	8 boys 14 to 15 years old	94 1	900 7	−4 4
19	6 old men	859 8	859 3	−0 1
21	7 dwarfs and legless men	695 6	68,	−1 1
26	5 normal men before and after breakfast	1 08 7	1 08 6	−0 0
20	4 normal men after caffeine	1 218 0	1 230 3	+1 0
	Sub-total normal controls	14 004 3	14 629 1	+0 2
7	10 typhoid patient	12 822 0	1 539 7	−2 2
14	11 hyperthyroidism patients	8 052 0	, 8 3 0	−2 9
14	1 cretin	4 2 1	479 2	+1 5
15	5 anemia patients	1 140 8	1 111 7	−3 3
16	16 cardiac patients	4 29 7	4 214 5	−1 9
17	6 diabetics	5 225 [illegible]	5 105 5	−2 3
24	3 diabetics	1 606 8	1 634 3	+1 8
22	10 nephritics	1 00 4	1 743 3	+2 5
23	1 patient with lymphatic leukemia	1 049 4	1 054 0	+0 5
28	5 malaria patients	2 91 2	2 592 8	+0 1
	Sub-total patients	38 907 0	38 298 0	−1 7
	Total normal controls and patients	53 571 3	52 927 1	−1 2

reactions or storages of substances or even hint that the law of conservation of energy may be distorted in disease The calorimeter has shown that the ordinary laws of nutrition will explain the processes in disease with the possible exception of certain phases of severe diabetes The law of conservation of energy applies just as strongly in the clinic as elsewhere Every new theory of metabolism must have its pluses and minuses balanced as carefully as the books of a banking house

ordinary method of having the nurse chart a record of fluids consumed and urine voided has an error of 600 to 700 or more cubic centimeters if it does not consider insensible perspiration, providentially balanced on the other side in patients on regular diet by the large amount of water contained in solid foods In the case of a sweating patient, who is too sick to eat much solid food, the routine chart is grossly misleading

The Table II illustrates the manner in which a patient with nephritis may eliminate more water through skin and lungs than through his kidneys

TABLE II

Lee H	Weight kg	Urine Vol c c	Fluid Intake c c	Water Vaporized from Skin and Lungs c c per day
Jan 5		260	1 278	514
6	61 5	240	980	
7		600	1 160	
8	60 7	040	1 140	

In four days fluid intake was 4 558 c c, urine, 2,040 c c, output of water through skin and lungs, 2,056 c c according to the two-hour experiment on Jan 5 The positive balance of 462 c c to the body was more than counteracted by a slight diarrhea and the patient actually was losing weight

By means of calorimeter experiments it has been possible to compare the water elimination of a large number of normal men and patients dressed in pajamas, covered with a blanket and exposed to a temperature of 22 to 25 C and a relative humidity of between 30 and 50 per cent Under such conditions normal men on an average excrete through skin and lungs about 700 grams of water a day losing in this manner 24 per cent of the heat produced Patients with high metabolism vaporize more water, but the increase usually is proportional to the total heat elimination Of course patients with falling temperatures lose a much larger proportion through vaporization from the skin The water losses of the insensible perspiration bear such a constant relationship to the total metabolism that they are now measured in some laboratories and clinics as a means of estimating the basal or even total heat production

Perhaps the most useful function of the calorimeter in clinical medicine has been to demonstrate that the methods of direct and indirect

calorimetry agree closely in pathological cases There has been a tendency for investigators to make rather wild speculations, when the results of respiration experiments with patients do not seem to follow the laws established with animals and normal men They assume abnormal

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Owing to technical difficulties the calorimeter does not always give close agreements between the methods of direct and indirect calorimetry in short periods or small groups of experiments A slight error is introduced when a patient is taken from a cool ward and placed in a warm respiration chamber and there is a tendency toward making the direct measurement a trifle too low This will be seen in Table III

A classical demonstration of the possibilities of the calorimeter was made by Benedict[10] *in the study of a man who fasted 31 days taking* nothing but distilled water In this case the data obtained before the fast were used as the basis of comparison The method of indirect calorimetry *demonstrated a marked reduction in total* metabolism The respiratory quotient proved that practically all carbohydrate was exhausted by the fifth day and that subsequently protein furnished 14 to

TABLE IV

BENEDICT S FASTING MAN

Subject I Height 170 7 cm Only distilled water was taken during this fast

	Day of Fasting			
	1st	11th	21st	31st
Body weight kg	50 60	53 88	50 49	47 39
Urine N gm.	10	10 25	7 93	6 94
CO_2 night c c per min	163	128	112	115
O_2 night c c per min	212	176	154	160
R Q night	0 78	0 72	0 73	0 72
H_2O per hour gm	22 8	18 3	14 6	17 9
Percentage of calories from protein	10 6	19 6	16 5	14 4
Calories indirect 24 hours complete rest	1 441	1 193	1 032	1 072 *
Calories indirect per sq m (height weight formula)	843	732	653	701 †
Calories per kilogram	24 2	22 1	20 4	22 6

*Previous day 1 023 calories

†Previous day 661 calories

20 per cent of the calories and fat the remainder Table IV gives a few of the many analyses made in this investigation which has thrown *much light on normal* and pathological conditions

In a severe case of diabetes mellitus the calorimeter will furnish a wealth of detail regarding the processes of metabolism when aided by careful urinary analyses This is shown *in the following* table (Table V) made from results obtained with a patient, Cyril K, nineteen years old[11] He was brought to Bellevue Hospital with the most severe type of complete diabetes his D N ratio showing that he was excreting in

the urine practically all of the glucose which could be derived from the protein molecule It was also possible to show that he was excreting in the urine maximal amounts of beta oxybutyric acid on December 15 and 16 After treatment by alkalies low diet and fasting he recovered from his dangerous acidosis and regained his tolerance for carbohydrates so that in the course of two months he was able to derive 6 per cent of his

TABLE V

METABOLISM OF PATIENT WITH SEVERE DIABETES (CYRIL K)

Period	Date	D N	R Q	Percentage of Calories from			Total Metabolism Variation from Average Normal	Urine Beta oxybut Acid
				Protein	Fat	Carbohydrate		
	1915							gm
1 First fasting	Dec 8-10	2 7						39 6
2 Mixed diet	11 14	1 9						56 5
3 High protein fat	15 17	3 9	0 ∞	23		0	− 11	77 8
4 Second fasting	18-21	2 7	0 14	18	81	1	− 2	45 7
5 Convalescence (interval two months)	22	1 1	0 734	20	4	6	−10	10 9
	1916							
6 Temporary recovery	Feb 10	0 0	0 915	31	7	62	−36	0 0

calories from carbohydrate It is interesting to note that the metabolism which was slightly higher than the normal when he was first observed dropped far below the average during the period of undernutrition

The examples that have been quoted serve to illustrate the type of information that can be obtained by the detailed study of an individual patient Physiologists and clinicians have extended the applications of calorimetry by studying large numbers of subjects in good health so that the normal limits are now fairly well established This has opened to other clinicians a method of laboratory diagnosis which has proved to be of considerable value

BASAL METABOLISM TESTS

Respiration chambers depending upon the method of direct calorimetry are too complicated for routine work in the clinic but the small

basal metabolism machines are fairly simple and are widely used now throughout the world There is a tendency on the part of clinicians to accept the results of the tests in a rather uncritical fashion Too many patients are sent to the laboratory without the proper preparation and the findings often are misinterpreted

Basal metabolism tests are of value in giving the clinician a better insight into the pathological physiology of disease, but their chief service is helping in diagnosis and treatment They differ from most laboratory tests in that they require the physical and mental cooperation of the patient Every clinician knows that he cannot obtain a basal pulse rate or respiration rate or even a good blood pressure reading unless the subject is quiet and mentally composed The basal metabolism test is more delicate than any of these Apprehension or discomfort will cause high readings even in trained subjects For example a physiologist in splendid mental and physical condition was undergoing a long series of metabolism tests which scarcely differed from day to day During the experiment for several days the subject was deeply concerned about a personal matter, and until this cause of worry was removed the metabolism tests gave high results With this emotional factor in mind one can imagine the results in a patient with Graves disease sent to a strange laboratory to find out whether or not she needs an operation!

The clinician should prepare the patient for the tests and the technician should be not only skillful but tactful and observant so that the report will include a note regarding the patient's comfort and state of mind An increased pulse rate during the test indicates discomfort or apprehension It is not enough for the clinician to glance at the part of the report which says "plus 50 per cent" and let it go at that He should ascertain the condition at the time of the test study the technician's note and check them himself by questioning the patient If he finds that the subject has slept poorly the night before has worried about the coming ordeal or has been uncomfortable during the actual test, he should become suspicious about the results and order a repetition

Standards of Normal Basal Metabolism

When the first normal standards were published in 1916 and 1917, there were available in the literature a few hundred individual measurements from various laboratories and the figures for children were scanty and much too high Now thousands of tests are made every week day and the technique has been greatly improved Good reports on large

numbers of normals have shown that the older standards of Aub Du Bois[12], Harris-Benedict[13], Dreyer[14] and Boothby and Sandiford[15] are 5 to 10 per cent too high Inasmuch as the majority of clinical reports in this country are made in terms of plus or minus deviations from these older standards there has been moderate confusion The situation is similar to the differences in standards for normal hemoglobin red blood cells blood sugar etc Clinicians fortunately are accustomed to 'standards that change and adjust themselves to a correction

Even with the best technique and one trained normal subject there is a considerable variation from day to day and year to year The extent of variation depends on the individual, figures 5 per cent from the aver age of many determinations on the same person are common, some vary as much as ± 10 per cent Boothby and his co-workers have emphasized the fact that basal metabolism as measured is not a lowest or fixed metabolism but rather a random sample observed under certain arbitrary defined conditions In many laboratories it is customary to take only the minimum value, but this violates a fundamental principle of random sampling

As a rule, three short basal tests are made and if they come within 5 per cent of each other the average is taken Some observers report only the two lowest figures that agree within 5 per cent excluding the high est on the ground that most errors in procedure tend to make results too high If the technique is satisfactory it is doubtful if this exclusion is justified since it tends to give a bias toward a lowered metabolism

Bearing in mind the variations in one and the same individual it is surprising that the variation among different individuals is only a little greater Jenkins in 193 worked out a table of probability of deviation of normal persons, and a few years later Berkson and Boothby[18] con structed the bell shaped Gaussian curves of the normal distribution and a nomogram showing the probability of the figures being within the normal range The large majority of normals come within 10 per cent of the average prevailing in the same laboratory a few are between 10 and 15 per cent and one or two in a hundred between 15 and o per cent This means that a reading of say + or — 18 per cent has about one chance in one or two hundred of being normal As a matter of fact most diagnosis is a matter of probabilities There are very few absolutely specific tests and even in these there is an occasional error in technic

The clinician s problem is to select the most practical set or sets of 'standards' and instruct his technicians how to use them It is advisable to have the reports made according to more than one standard This

helps to detect errors in calculation, and it emphasizes the variability In this country the majority of the reports are now made according to the Mayo Clinic standards of Boothby, Berkson and Dunn[1], which after the age of 20 are slight modifications of the older Aub and DuBois, Boothby and Sandiford levels The Harris Benedict figures average 3 to 4 per cent lower Krogh's standards which subtract 6 per cent from the Aub and DuBois come very close to the present reports from many laboratories According to the careful work of W H Lewis[18] on 100 old men the Aub and DuBois curve is a trifle high

When it comes to children, the Aub and DuBois curve is much too high and the Mayo figures better but still a little high There have been many excellent reports on children, well summarized by R C Lewis Kinsmann and Iliff[19, 19( ), 19(b)] The large series of children studied with the utmost care over many years by Lewis and his associates in Denver probably gives the best picture of the curve of metabolism in childhood They have shown that the peak of metabolism must come before the second birthday, since after that age there is almost steady decline with a small relative increase before puberty that gives a short plateau The standards for the ages from 2 to 15 years have been published by Lewis, Duval and Iliff[0] Probably there are not many laboratories that can secure such good results with children and such low figures It is suggested that for children both the Lewis and Boothby, and Berkson and Dunn standards be used in reports

The first day's tests on patients should be regarded with suspicion The patient is often tense with apprehension and excited by the novelty of the surroundings and the first experience of breathing into a machine He tries too hard and fails to relax Therefore, the first test may be 5 or even 20 per cent or more higher than subsequent tests This error is not frequent with normal controls Therefore, with patients particularly those who are apprehensive, it is advisable to discard the first day s test unless it is clearly within normal limits In a series of tests the first day should never be used as a base line, and reports from other laboratories must be employed with caution unless one is sure of the technic and the standards on which the plus or minus estimates are based

In view of local differences of procedure it is best for each laboratory to check its own normal level and determine its zones of normal limits It may be found for example that 90 per cent of the normal controls will fall between + 6 per cent and − 16 per cent according to the Harris Benedict or Aub and DuBois standards An extension of six 5 per cent in either direction usually will include 98 per cent of the normals In

reporting any individual case the technician, therefore will be able to state not only the actual calories per day, or better calories per square meter per hour and the percentage of deviation from a given standard, but also whether or not the patient is within the normal zone for that clinic.

Most of the factors which influence basal metabolism are taken care of in the routine procedure. The requirement that the patients must be tested at least 14 hours after the last meal usually removes the stimulating influence of food, although heavy over feeding on the previous day may show its effect for a longer period. The requirement that the subject shall avoid undue exertion in coming to the laboratory and shall lie down for at least half an hour usually is sufficient to remove the effects of muscular exercise, but patients who are seriously ill require a longer period and it is better to have them spend the night in the hospital. The Aub and DuBois and the Boothby standards which are based on surface area and also the Harris-Benedict standards take care of differences in weight, height, age and sex, all of which influence metabolism in varying degrees. For all other factors the clinician must make his own allowances.

In women the small rise in metabolism which occurs a few days before the onset of menstruation usually is disregarded. It is variable, seldom more than 3 to 5 per cent, but probably greater in women with marked subjective symptoms. The onset of puberty in some girls is a period of considerable rise in metabolism. Apparently the menopause and estrogenic therapy have but slight effect.

There are certain other factors found in normal persons and patients which must be considered. Numerous reports in the literature from all over the world regarding the effect of race have been well reviewed by Albagli[1, 11] and Wilson. Most of them show figures 5 to 10 per cent lower than the older standards, but as we have said before, similar figures have been obtained in the large majority of the recent publications in the United States. The low basals found in the Orient and the tropics probably are due to poor nutrition with low caloric and protein intake. There still remains the possibility of a slight racial or environmental lowering of metabolism in the tropics, and a few reports indicate a higher metabolism in isolated races of Indians.

Therefore, in the clinical interpretation race may be disregarded, but attention should be paid to inanition which in extreme cases can lower metabolism 40 or more per cent. Thin persons in good condition, obese patients and people with unusual build come within the normal standards

based on surface area but not within standards based on height or weight alone This is the chief reason for using surface area

If a patient has an elevated temperature at the time of the test, it should be remembered that there is a rise in metabolism of about 13 per cent for each degree Centigrade or 7 2 per cent for each degree Fahrenheit Dyspnea in patients with decompensation naturally gives results that are falsely high, especially if a patient with orthopnoea is measured in the routine flat bed Most errors are on the plus side but if a patient who is not watched falls asleep the results will be about 10 per cent low This shows that the so-called basal metabolism is not synonymous with minimal metabolism

There are several diseases beside those concerned with the thyroid gland which show alterations in basal metabolic rate They have been listed by Boothby and Sandiford[3] Among the most important raising heat production are leucemia pernicious anemia, cardiac decompensation with dyspnea, fevers, some cases of high blood pressure and certain phases of pituitary disease Low readings are obtained in malnutrition some cases of nephrosis, Simmons disease and some types of pituitary dysfunction Fortunately most of these are easily recognized Moderately low readings of about minus 20 occur in a puzzling group of neurotic patients with low vitality Some of these are helped by thyroid substance but others show no response An excellent review of energy metabolism with 383 references has been published in 1946 by Peters[4]

Basal metabolism tests are of relatively little value in the estimation of the total caloric requirement for the 24 hours It is difficult to judge the increases due to activity and the decreases due to sleep The stimulating effect of food the specific dynamic action usually amounts to 6 to 8 per cent of its caloric value During periods of moderate activity the heat production may be 20 to 100 per cent above the basal In severe exercise the metabolism is increased tenfold Basal conditions obtain for only a few hours, and the calculation for the remainder of the day is guesswork

From a clinical standpoint basal metabolism tests are chiefly of value as an aid in the estimation of thyroid activity Patients with severe Graves disease give results 50 to 100 per cent or more above normal Patients with severe myxedema average about 40 per cent below normal In milder cases the readings are roughly proportional to the extent of the hyper- or hypo- thyroidism

Perhaps the best evidence that the basal metabolic rate indicates the level of thyroid activity is found in a paper by Means and Lerman[5]

They have shown that the curve of the fall in metabolism, curve of decay, is similar in shape and time after thyroidectomy, the administration of iodine in Graves' disease, after withdrawing thyroid medication in myxedema or in patients made artificially thyrotoxic. The curves obtained by Means and Lerman closely approximate the thyroxine decay curve of Boothby. Of course the basal metabolism test must not be taken too literally, as there are many exceptions to the general rule. It is only one of many tests and no laboratory report can be used without the admixture of a large amount of clinical judgment.

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CHAPTER IX

RESPIRATION IN DISEASE

BY FRANCIS W PEABODY

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BEFORE taking up the subject of the respiration in pathological conditions it may be well to consider briefly a few facts concerning normal breathing and the methods by which the respiration responds to any unusual demands that may be made upon it It is in general customary to separate sharply the internal respiration between the tissues and the blood from the external or ' pulmonary respiration between the blood stream and the air outside the body Such a distinction is however justifiable in only a limited sense and although serving a purpose it tends to obscure the broader point of view from which the subject should properly be approached In attempting to analyze too minutely the different phases of the respiration the student of physiology or of physiological pathology is liable to lose sight of the fact that he is in reality investigating not a single independent function but a group of interacting functions each influencing and being in turn influenced by the other This intimate relationship and interdependence exists not only between the various functions of the respiration but also between the respiration as a whole and the circulation of the blood

It is indeed perhaps unfortunate that the respiration and the circulation are so generally regarded and studied as separate entities for a better understanding of each would result if attention was more frequently focused on what might be termed the circulatory respiratory mechanism Up to a certain point the circulation and the respiration must be studied separately and the various details of each require intensive investigation along more and more sharply defined lines if the limits of our knowledge are to be expanded But when as clinicians we approach the problem of disease it is essential to look at the organism

as a whole and to appreciate how closely the various physiological functions are interrelated In the normal living organism respiration and circulation go hand in hand Thus for instance the blood carries the hormone of the respiration to the medulla and the stimulation of the respiratory center causes an increase in the pulmonary ventilation This increase in ventilation helps to supply the coronary vessels of the heart with a normal blood and it also exerts a direct action on the circulation by facilitating during inspiration the blood-flow from the great veins to the right side of the heart But behind the circulation and the respiration, dependent on them and at the same time the most important factor in their regulation lie all the complex chemical processes which go on in the tissues and which are customarily summed up under the general caption of the *metabolism* The continuation of life itself is determined largely by the carrying on within certain rather definite normal limits of the metabolic processes of the body cells and the normal activity of these metabolic processes is in great degree dependent on the adequate provision of oxygen and on the adequate removal of carbon dioxid Under normal conditions the body metabolism is probably at its lowest ebb during deep sleep but for purposes of general comparison the usually adopted standard is the so called *basal metabolism*—the metabolism when the body is at complete rest and when the digestive processes are at a minimum Under these conditions the contraction of the heart and the tonus of the blood vessels are so regulated as to provide sufficient oxygen to meet the needs of the cells and to remove the carbon dioxid that results from metabolic activity At the same time the movements of the lungs are regulated so that the rate and depth of respiration is such as to provide in an economical manner the entrance into them of sufficient atmospheric air to insure the proper saturation of the blood with oxygen and the discharge from it of excess carbon dioxid But during the course of normal life there are many factors—such as the taking of food muscular movement or nervous activity—which increase the metabolism and thus create an increased demand for oxygen on the part of the cells involved To this increased demand the organism responds by a complex series of adjustments on the part of the respiration and circulation which are aimed at allowing the body to carry on its activities at the new higher level The changes in the circulation are such as to increase the blood flow In general they consist in an increase in the rate of the heart an increase in the output of the heart per beat, a rise of blood pressure and vascular contraction or dilatation in the various parts of the body As a result of this the blood flow through the lungs is augmented More blood passes through the pulmonary

vessels and the time during which the blood is in the pulmonary capillaries is decreased In order therefore that the blood shall be adequately aerated the composition of the air in the alveoli of the lungs must be kept such that its oxygen tension is high enough to saturate the increased amount of hemoglobin which passes the lungs in a decreased time and the carbon dioxid tension must be kept so low that the increased amount of carbon dioxid in the venous blood will diffuse out readily into the air of the alveolar spaces To accomplish this the air in the lungs and especially that in the alveoli must be more completely diluted by atmospheric air This is brought about by increasing the rate and the depth of respiration—both of which actions increase the volume of air entering the lungs in a given time or the so called *minute-volume* of pulmonary respiration

These adjustments may be brought about with astonishing rapidity as is seen at the onset of severe physical work The response of the circulation is probably initiated and perhaps regulated by nervous reflexes That of the respiration is directly regulated by the metabolic processes themselves for the stimulus to the respiratory center is the increase of the H ion concentration of the blood It would appear that these adjustments to an increase of metabolism are adapted to the needs of the organism in an astonishingly accurate and economical manner Blood flow and pulmonary ventilation are raised to fulfill the demands of the tissues but not much beyond these demands and there is a harmonious interrelation between the increase of blood flow and that of pulmonary ventilation No considerable increase of body metabolism could be met by increasing the blood flow or the pulmonary ventilation alone When however the circulation and the respiration are functioning normally the metabolism may be raised four or five times and in trained persons nearly ten times above the basal value without the organism suffering from an insufficient supply of oxygen or from an accumulation of carbon dioxid It will thus be seen that the reserve on the part of the respiratory circulatory mechanism is comparatively great

Conditions analogous to those which have just been mentioned are also met with in the various pathological states which are associated with an increased metabolism Febrile diseases and hyperthyroidism are the conditions which are perhaps most definitely characterized by increased heat production but the same thing to a lesser extent or less constantly may be found in diabetes anemia advanced nephritis and various other diseases Here again the body meets the increase of metabolism in the normal way by increasing the rate of blood flow and of pulmonary ventilation Inasmuch as the increase of metabo

lism due to disease is rarely more than 100 per cent above the normal basal value it is comparatively easy for the body to meet the demands of the tissues as long as the circulation and the respiration are normal Various other abnormal conditions such as acidosis oxygen lack and nervous influences behave in a manner similar to an increase in metabolism and stimulate the respiratory center The result is again an increase in minute volume of pulmonary respiration At the same time there are other pathological conditions which prevent the organism from responding to these stimuli and which limit the degree to which the minute volume can be raised An increase in minute volume is brought about largely by increasing the volume of each respiration and so it is that those factors which prevent deep breathing are important in the pathology of the respiration These influences manifest themselves in various ways but chiefly by causing a diminution in the vital capacity of the lungs What may be termed the "reserve of the pulmonary respiration—its power of responding to demands over and above what is required at rest—may be expressed by the difference between the ventilation of the lungs at rest and the highest degree of pulmonary ventilation which the subject is capable of maintaining

Under normal conditions, with the body at complete rest the movements of the thorax and diaphragm are such that about four or five liters of air enter and leave the lungs per minute, and this is sufficient for the gaseous requirements of the body When the metabolism is increased so that the body needs greater amounts of oxygen and larger quantities of carbon dioxid must be removed the respiratory center is stimulated with the result that the rate and more especially the depth of breathing is increased By this means the volume of air breathed per minute (the *minute-volume*) can be enormously increased When walking quietly the pulmonary ventilation is two or three times what it is when lying down and in some observations made on healthy young men it was found that when riding a bicycle at a high rate of speed the minute volume of air breathed averaged nearly ten times what it was while they were sitting on the bicycle at rest This gives a rough index of the normal reserve' of the pulmonary respiratory mechanism Many of the pathological conditions affecting the respiration act essentially by reducing this reserve and it is evident that they may do so either by increasing the minute volume of air breathed while at rest or by decreasing the maximum minute volume which the patient is capable of breathing These two influences will be considered under the headings of 'The Minute Volume of Pulmonary Ventilation' and "The Vital Capacity of the Lungs' In addition to these certain other conditions bring about interesting and important Irregularities of the Respira

tion When one considers these various abnormalities it is important to remember that disturbances of the respiration the circulation and of the blood itself often go hand in hand and it is only by a somewhat arbitrary distinction that the present discussion is limited to the external respiration

THE MINUTE VOLUME OF PULMONARY VENTILATION

The most common form of abnormal respiration met with in disease is *hyperpnea* or an increase in the amount of air breathed per unit of time above the normal value for the subject when at rest Hyperpnea may be due to an increase in the depth of respiration or in the rate of respiration or it may be due to a combination of the two If the abnormality is essentially one of rate one may speak of a *tachypnea* or *polypnea* It is important however that *hyperpnea* should not be confused with *dyspnea* *Dyspnea* as the derivation of the word indicates is a difficult or labored breathing and there is implied in it an element of subjective discomfort This subjective distress apparently arises from the fact that either the circulation or the respiration or both are not able to keep pace with the gaseous requirements of the body The reserve power of the circulation or respiration has been used up In so far as dyspnea is dependent on the respiration it is caused by an inadequate aeration of the blood in the lungs This may be due to several causes one of which is an inability of the subject to increase his pulmonary ventilation sufficiently to produce an adequate degree of hyperpnea Dyspnea is usually associated with hyperpnea but whether in a given instance hyperpnea is associated with dyspnea will depend on the degree to which the pulmonary ventilation is increased and on the ability of the subject to raise his minute-volume to that degree easily

There are various factors which may cause an increase in the minute volume of pulmonary respiration Thus it may be brought about by an increase of metabolism whether this be due to a physiological process as exercise or to a pathological process as in Graves disease Hill and Flack ([1]) have shown the effect of temperature in raising the ventilation by immersing subjects in a hot bath at a temperature of 105° to 110° F The minute volume rose to 20 or 30 liters and even in one instance to 50 liters Another type of hyperpnea is that caused by stimulation of the respiratory center in pathological conditions associated with acidosis Hyperpnea is also seen frequently in various nervous disturbances such as hysteria

Closely related to the subject of pulmonary ventilation is the question of *alveolar ventilation* or the volume of air which actually reaches the alveolar spaces per minute From the point of view of the respiratory

exchange the important thing is, not how much air enters the mouth and nose in a given time but how much air enters the alveoli of the lungs and is able to take part in the gaseous exchange with the blood With each breath a part of the air inspired remains in the buccal and nasal cavities in the larynx, trachea, and bronchi This portion of the inspired air does not take part in the respiratory exchange of gases, and the area which it occupies is known as the *dead space* Haldane ([1]) and Henderson Chillingworth and Whitney ([2]) have shown that the dead space for oxygen is larger than that for carbon dioxid, and the latter explain this on the basis that considerable amounts of carbon dioxid may diffuse out from the blood in the walls of the respiratory passages The dead space is to be regarded as a physiological, and not as an anatomical conception As Haldane says (*loc cit*) ' The magnitude of this space depends on the physiological efficiency of the respiratory surface in relation to the supply of venous blood and fresh air' Much work has been done on the determination of the size of the dead space, both with normal respiration at rest and under various conditions such as hyperpnea but the results obtained by different investigators are not in harmony The generally accepted value for the dead space in normal persons at rest is not far from 120 to 140 c c The authors just cited agree in finding that the dead space is much larger when the respirations are deep, either at rest or with exercise, but Pearce ([4]) states that he found only a small variation in the dead space between the conditions of rest and exercise consisting of walking 3½ miles an hour and Krogh and Lindhard ([5]) say that with the maximum inflation of the lungs the increase in the size of the dead space may amount to 100 c c.

Until the vexed question as to the size of the dead space in normal individuals is definitely settled, it is perhaps best to be somewhat skeptical with regard to the observations which have been made on it in pathological conditions Such determinations as have been made however indicate that there may be a considerable change in the dead space in different diseases Thus there is good evidence to show that the dead space is increased in emphysema An increase in the size of the dead space is a factor which may cause hyperpnea because with a large dead space there will be less of each individual respiration that will reach the alveoli than with a small dead space If, for instance a subject breathes 10 times a minute and each respiration is of 400 c.c his total minute volume is 4 000 c c With a dead space of 120 c c only 280 c.c of each respiration will take part in the gaseous exchange and the alveolar ventilation will therefore equal 280 × 10 or 2 800 c c per minute This is presumably the amount of alveolar ventilation required by the metabolic activities of the body If then the dead space were

increased to 200 c c only 200 c c of each respiration of 400 c c would reach the alveoli and the minute volume of alveolar ventilation would be 200 × 10 or 2 000 c c. But this is below the needs of the body and the ventilation must be raised so as to compensate for the increase in dead space This may be done by increasing the rate or depth of breathing If the volume per respiration is kept constant at 400 c c. the requisite alveolar ventilation will be obtained if the rate is increased to 14 per minute (400–200 × 14 = 2 800) but the total minute volume will then be 5 600 c.c On the other hand if the rate is kept constant the necessary alveolar ventilation will be reached if the volume of each respiration is increased to 480 c c. (480–200 × 10 = 2 800) In this case the total pulmonary ventilation will be 4 800 c c It will be seen that an increase in the size of dead space necessarily brings about a hyperpnea in order that the alveolar ventilation may be maintained but the hyperpnea will be less in degree if compensation is brought about by increasing the depth of respiration than if it is done by increasing the rate of respiration The dead space may also be an element in the production of hyperpnea in cases where the respiratory surface is cut down as occurs when a large pleural effusion compresses one lung In such an instance the area of the dead space is not affected but the proportion of each inspiration that remains in the dead space is larger than normal The result will again be that the necessary alveolar ventilation must be obtained by the development of an increased pulmonary ventilation

Strictly speaking it would of course be of greater clinical significance to determine the alveolar ventilation than it is to determine the total pulmonary ventilation for it is the former that takes an active part in the exchange of gases with the blood Hitherto however this has not been very practicable The calculation of the alveolar ventilation involves a knowledge of the size of the dead space and the methods for obtaining this are too complicated and difficult to apply extensively to patients There is also as has been indicated some doubt as to their reliability The alveolar ventilation may of course be calculated by assuming a normal or standard figure for the dead space but especially in pathological conditions such an assumption may be far from accurate and may lead to large errors Until therefore more information is gathered concerning the dead space in normal persons and in disease it may be best to devote attention chiefly to the total ventilation —a value that can be readily determined

The method of determining the total pulmonary ventilation is on the whole very simple The subject should lie at rest in bed for at least 15 minutes before the observation is begun It is only for the most

highly accurate and strictly comparable results that it is necessary that he should be in the fasting state required in basal metabolism observations but it is on the whole better not to make determinations within one or two hours after a hearty meal The subject is then made to breathe through valves separating the inspired from the expired air and the latter is measured for a known period of time The best way to collect the expired air is in a large (100 liter) spirometer but as accurate results can be obtained if the expired air is allowed to pass through a carefully calibrated gas meter When patients cannot be moved to the laboratory it is often convenient to collect the air in a Douglas bag (*) and then measure it by passing it through a gas meter In order to avoid any error due to the breathing being uneven from minute to minute the expired air should be measured over a period of at least 5 minutes Results that are comparable from one patient to another are best obtained if the temperature of the expired air and the existing barometric pressure are taken and the volume of air reduced to standard temperature and pressure conditions dry (0° C and 760 mm) The chief difficulty consists in the fact that it is not always easy to collect the expired air without interfering to some degree with the normal respiration of the subject The easiest way is to have the valves attached to a rubber mouthpiece with a tube to breathe through about 1 5 cm in diameter, and a wide flange to fit between the teeth and cheeks to prevent leakage The nose is then closed with a clip This method has the disadvantage that most people do not breathe naturally through their mouths and when the nose is closed they have a tendency to overventilate It is therefore better to use some form of mask which covers both mouth and nose, and allows the subject to breathe through either Even with this arrangement some trouble is often found with nervous patients and especially with patients who are dyspneic and who fear that the apparatus may cut off some of the air It is in all cases essential that the subjects should breathe through the apparatus for some minutes before the measuring of the air is begun so that they may get used to it and may get over any abnormalities of respiration which may arise when the apparatus is first applied

The rate of respiration is most accurately determined by means of a pneumograph attached to the patient's chest, and registering by a simple tambour on a revolving drum The time intervals should be marked on the drum by some form of time marker Having thus obtained the volume of air expired over a known period of time and the rate of respiration the minute volume of ventilation and the volume per single respiration can be calculated

The normal figures for the minute volume of pulmonary ventilation

show a considerable amount of variation depending largely on the size of the individual Even with the same alveolar ventilation the pulmonary ventilation in the same individual will vary somewhat according to whether he is breathing slowly and deeply or rapidly and superficially There is thus no such close relationship between pulmonary ventilation and body surface area as there is between the latter and basal metabolism Sufficient accurate data are not at hand to enable us to know whether there is a close relation between alveolar ventilation and body surface area. The average minute volume of pulmonary respiration for adults at rest is between 4 and 6 liters measured at standard temperature and pressure dry Debenham and Poulton (7) have made careful observations on 10 normal men and give as their results figures from 4 87 to 7 55 liters The average is 6 06 liters These volumes are however measured at 37 C and prevailing atmospheric pressure saturated with moisture Reduced to 0° C dry the average minute-volume would be about 5 0 liters The subjects of these observations were studied while resting on a bed and in the fasting state Schlesinger and Pembrey (8) found the average minute volume to be 7 105 liters uncorrected for temperature in a group of medical students who were examined during the course of their usual day s work

Debenham and Poulton give as the mean tidal air (volume per respiration) 410 c c with a maximum of 524 c c and a minimum of 310 c.c. Corrected to standard temperature and pressure the average would be about 335 c c The same authors also determined the dead space in their subjects and calculated the average alveolar ventilation as 3 94 liters per minute

Hyperpnea may occur in pathological conditions as the only or the chief abnormality of the respiration or it may be one factor in a clinical picture which is complicated by other processes interfering with the pulmonary respiration As an uncomplicated feature it is most often seen in association with an increase of metabolism an acidosis or in certain conditions which are probably of a nervous origin

Investigations of the gaseous exchange have shown that an increase of *metabolism* may be present in many pathological conditions No attempt will be made to consider all of these but some of the more important may be referred to Thus many observations have shown a rise of the basal metabolism in *fever* Typhoid fever has perhaps been as thoroughly studied as any febrile disease and Coleman and Du Bois (9) state that the average increase is approximately 40 per cent although figures over 50 per cent are frequently encountered A rise in metabolism may also take place in *anemia* Meyer and Du Bois (10) found an increase of 7 to 33 per cent in the oxygen consumption in two severe cases of anemia with a hemoglobin percentage of less than

25, but in two milder cases, with a hemoglobin percentage between 40 and 44 there was no definitely pathological increase in metabolism In *leukemia* the metabolism may be much above normal, and the increase appears to be rather closely parallel to the rise in the leucocyte count The increase in metabolism is not to be accounted for by the degree of anemia Thus in Case 5 (Table I) the metabolism was 20 per cent above normal at a time when the hemoglobin was 75 per cent and the leucocyte count about 90 000, and in Case 6 the metabolism was 65 per cent above normal when the hemoglobin was 50 per cent and the leucocytes numbered approximately 950 000 The basal metabolism has also been studied in many cases of *exophthalmic goiter,* and in general it has been found that there is a close relationship between the rise in metabolism and the severity of the disease In marked cases the metabolism rises to a higher degree in this condition than in any other disease that as yet has been investigated carefully In Table I are given the results obtained in the study of the basal metabolism of cases of exophthalmic goiter and myelogenous leukemia at the Peter Bent Brigham Hospital The expired air was collected in a large Tissot spirometer and the metabolism calculated in the usual way on the basis of oxygen consumption and respiratory quotient These cases enable one to see definitely the relation of increased metabolism to hyperpnea for it was possible to make observations showing great variations in the metabolism in the same individual In the patients with exophthalmic goiter the fall in basal metabolism followed in three instances an operation for thyroidectomy and in the patients with leukemia it followed radium treatment which brought their leucocyte counts down to normal figures It will be noticed that the pulmonary ventilation increases with the rise in metabolism but there is no very definite relationship between the two The extent to which the increase in minute volume of air breathed depended on an increase of rate or of depth varied in the different cases It is especially noteworthy that even with the highest figures for basal metabolism the minute volume was not as much as twice what it was when the metabolism was normal The "reserve of the pulmonary mechanism is so great that the minute volume can be doubled easily if the lungs are normal It is unlikely therefore that a rise in metabolism uncomplicated by other features is in itself an important factor in causing dyspnea while a patient is at rest Its chief significance is when it is associated with other conditions which interfere with the respiration and also on account of the fact that the increased minute volume at rest serves to cut down the 'reserve" which will be called on when any further demands such as occur in exercise are made on the respiratory system

TABLE I

RELATION OF PULMONARY VENTILATION TO METABOLISM

(Metabolism is expressed in percentage of normal according to the standards of age and surface area of Du Bois)

Case No	Diagnosis	Age	Sex	Metabolism in per cent of Normal	Minute Volume Liters S T P D	Rate of Resp	Volume per Resp c.c.	Pulse Rate	Remarks
1	Exophthalmic Goiter	21	M	+83 +65 +22	9.32 7.67 6.16	24.1 20.9 16.3	388 367 379	127 129 88	After thyroidectomy
2	Exophthalmic Goiter	19	F	+31 − 6	6.46 4.54	22.7 18.4	285 247	81 69	
3	Exophthalmic Goiter	25 28	M	+73 +46 − 4	11.10 8.51 6.16	15.9	353	135 118 88	After thyroidectomy
4	Exophthalmic Goiter	38	M	+69 + 3	8.84 5.32	21.3 17.8	415 298	128 78	After thyroidectomy
5	Myelogenous leukemia	29	M	+20 − 9	6.52 4.8	14.3 11.8	456 355	75 60	After radium treatment
6	Myelogenous leukemia	26	M	+65 +36 +12	9.75 7.56 6.16	12.3 15.4 12.8	796 492 484	80 68 63	After radium treatment

In connection with the hyperpnea associated with the increase of metabolism in fever mention may be made here of an unusual degree of hyperpnea which is occasionally seen in the *late stages of severe acute infections*. This is illustrated by two patients observed at the Peter Bent Brigham Hospital. The first was a middle aged woman with a marked unilateral exophthalmos which with other signs led to the diagnosis of thrombosis of the cavernous sinus. On the day after admission to the hospital she was comatose and the breathing showed an extraordinary hyperpnea. Respiration was regular. Each individual breath was much deeper than normal and the rate of respiration was 50 per minute. The minute volume could not be measured but it is scarcely possible that it was less than 20 to 25 liters per minute. The temperature was 105° F, the pulse rate was 160 per minute, the hemoglobin was 90 per cent

and the leucocyte count was 24 000 per c mm The deep regular respiration suggested that seen in severe diabetic acidosis, except that it was more rapid than is usually the case in that condition The carbon dioxid tension in the blood by the Van Slyke method was however 26 6 mm This figure is somewhat below normal, but does not indicate a degree of acidosis which could at all account for the hyperpnea It seems more probable that the low value was the result of the hyperpnea, and the washing out of carbon dioxid from the blood The breath sounds were heard all over both sides of the chest but there were harsh breathing and a few rales at the left base posteriorly This was taken to indicate a beginning pneumonia, but the involvement of the lungs was slight and not such as to explain the hyperpnea There was no cyanosis The spinal fluid was cloudy and contained 1 800 leucocytes per c mm The blood culture was positive for staphylococcus albus On the following day the patient died An exactly similar picture occurred at the end of a long protracted case of cerebrospinal meningitis, at a time when there were signs suggestive of an early pneumonia at the right base behind The rate of respiration was 46 per minute the volume per respiration was 479 c c and the minute volume was 22 3 liters When completely saturated with oxygen the blood contained 19 3 volumes per cent, and the oxygen content of the venous blood was 7 22 volumes per cent The hemoglobin was 90 per cent The carbon dioxid tension of the blood was 23 1 mm indicating only a moderate degree of acidosis—wholly insufficient to account for the hyperpnea The temperature was 102 5° F The blood culture was negative Conner and Stillman ([11]) mention the occurrence of this type of dyspnea in their studies on the respiration in meningitis Very rapid regular breathing was a constant terminal phenomenon in fatal cases The cause of this extreme hyperpnea seen occasionally in cases of severe acute infection is not clear

The respiratory center is extremely sensitive to any increase in H ion concentration of the blood, and one of the most characteristic evidences of the development of an *acidosis* in the organism is the production of hyperpnea The effect of acidosis on the respiration has been most carefully studied in reference to *diabetes* in which there may be a great production of β oxybutyric and of aceto acetic acid These acid bodies are neutralized by combination with the fixed bases of the blood and tissues and on account of the large amount of so called "buffer salts" in the blood comparatively great quantities of acid may be produced without the actual reaction of the blood being shifted When however a certain point is reached and the accumulation of acids in the blood is so great that the reaction of the blood begins to change, the increase of acidity stimulates the respiratory center As a result of this the

minute volume of air breathed is increased more carbon dioxid is washed out of the blood and the increase of non volatile acids in the blood is compensated for by a decrease in carbon dioxid so that the final reaction of the blood remains unaltered It is probably only in the terminal stages of fatal cases that the actual reaction of the blood changes At other times the acidosis is recognized by the decrease in carbon dioxid tension of the blood Minor degrees of acidosis such as cause a slight fall in the tension of the carbon dioxid of the blood bring about a slight rise in the minute volume of air breathed while the higher degrees of acidosis in which the carbon dioxid tension falls from the normal of approximately 40 mm to 15 or 10 mm cause an intense hyperpnea It is with these low carbon dioxid tensions that one sees the very deep respiration which is typical of air hunger or the so called Kussmaul breathing In such cases the minute volume is often from 20 to 30 liters In diabetes the acidosis is due primarily to an excessive formation of acids but a similar result occurs in nephritis in which an acidosis may be brought about owing to an inability to excrete acids normally Mild degrees of nephritis are usually not associated with an acidosis sufficient to cause decrease in the tension of the blood carbon dioxid but in advanced cases with an output of phenolsulphonephthalein less than 10 per cent in two hours a low carbon dioxid tension may be found In cases of uremia the carbon dioxid tension may fall to below 10 mm and in such cases a marked hyperpnea develops with deep respirations exactly similar to the air hunger seen in diabetic coma ([12]) Air hunger dependent on acidosis accompanied by very low carbon dioxid tension has been described by Howland and Marriott ([13]) in severe intestinal conditions with diarrhea in children and by Sellards ([14]) in the marked acidosis of cholera Slight degrees of acidosis may occur in many conditions such as pneumonia ([15]) and other febrile diseases as well as in starvation and in persons on a diet low in carbohydrates ([16])

The degree to which hyperpnea may develop as a result of acidosis is indicated by observations on a patient with nephritis studied at the Peter Bent Brigham Hospital The case was unusual in that a marked disturbance of respiration amounting to true dyspnea arose rather suddenly in a man with an acute nephritis and a phenolsulphonephthalein output of 19 per cent in two hours The blood urea nitrogen was 44 mg per 100 c c blood The patient was perfectly conscious with deep slightly rapid respiration The rate of respiration was 26 per minute and the minute volume of air breathed was 24 2 liters The average volume per respiration was thus about 1 200 c c The hyperpnea in this case was however not as marked as is frequently seen in diabetic coma

The effect of lesser degrees of acidosis on the minute volume of respiration is illustrated in the following table compiled from cases studied by Higgins Peabody and Fitz (*loc cit*) in a study of the acidosis developing in men on a diet low in carbohydrates The extent of the acidosis is indicated by the fall in the tension of carbon dioxid in the alveolar air

TABLE II

Case No	Alveolar CO_2 Tension m m	Minute Volume Liters S T P D
1	38 6 29 1	4 99 6 98
2	38 7 30 1	4 55 5 73
3	38 1 35 7	4 91 6 00

The hyperpnea due to acidosis may be decreased by the administration of alkali, and if sufficient alkali is given to raise the carbon dioxid of the blood to a normal value the hyperpnea will usually disappear The effect of alkali on the hyperpnea of acidosis is shown in Table III The patient was a man with advanced chronic nephritis and beginning uremia The urea nitrogen was greatly increased there being 106 mg per 100 c c blood After the first observation was made 80 grams of sodium bicarbonate were given This was enough to change the reaction of the urine from acid to alkaline At the same time the blood carbon dioxid tension rose from 23 to 52 mm and the minute volume fell from 6 36 to 4 06 liters It is doubtful whether the slight rise in basal metabolism is of any significance but it is noteworthy that this rise was associated with a fall in minute volume

TABLE III

Date	Metabolism*	Minute Volume Liters S T P D	Rate of Resp	Volume per Resp c c.	Pulse Rate	Carbon Dioxid Tension of Blood mm
Apr 11	−9	6 36	13 7	464	69	23
Apr 15	normal	4 06	15 2	268	82	52

* Metabolism calculated according to body surface and referred to normal standards of Du Bois

Much more striking results are of course achieved when alkali is given to patients with higher grades of acidosis Table IV illustrates the effect of the administration of 120 grams of sodium bicarbonate to a man in early uremia with a carbon dioxid combining capacity of 17 6 volumes per cent In this patient there was practically no excretion of phenolsulphonephthalein in two hours The total non protein nitrogen of the blood was 1,5 mg per 100 c c the hemoglobin was 54 per cent and the vital capacity was 1 900 c.c

TABLE IV

CO Combining Capacity vols per cent	Minute Volume Liters	Respiration Rate	Volume per Resp c.c.	Pulse Rate
17.6	15	[illegible]	730	98
60 7	[illegible]	2	200	

In the conditions that have just been described the acidosis was due to the increased production or to the retention of non volatile acids That a similar hyperpnea may be brought about by an *acidosis due to carbon dioxid* has been shown experimentally by Scott ([22]) in observations made on decerebrate cats breathing air containing increasing percentages of carbon dioxid His results indicate that a true carbon dioxid acidosis may exist That a similar condition may occur clinically has been indicated by Peters ([1]) and Peabody ([2]) Both of these observers have found that in certain cases of acutely decompensated heart disease with dyspnea and usually with cyanosis the carbon dioxid tension in the venous blood may be considerably higher than it is in the alveolar air This is probably due to an interference with the passage of carbon dioxid from the blood into the alveolar air On the other hand observations by Hurter ([20]) on the arterial blood gases failed to show any abnormal increase in the carbon dioxid in several patients with decompensated heart disease chronic bronchitis pulmonary tuberculosis or pleural exudate If a retention of carbon dioxid did occur it would cause an increase in the H ion concentration of the blood which would stimulate the respiratory center and would be a factor in the production of dyspnea

With regard to *methods for the determination of acidosis* little need be said in this place as they are now generally well known to clinicians The subject has recently been admirably reviewed by Sellards ([21]) who also describes the details of various methods Direct determinations of the H ion concentration of the blood are most accurately performed by

electrochemical methods, but the technique is extremely difficult and the variations in blood reaction are so slight that no actual change is usually found except in severe cases just before death The simplified dialysis method of Levy, Rowntree and Marriott ([22]) is comparatively easy to carry out but it is less satisfactory than the indirect methods depending on the determination of the carbon dioxid tension of the blood The actual reaction of the blood remains remarkably constant during life and as the amount of non volatile acid in the blood rises there is a compensatory fall in the carbon dioxid The determination of the degree of the decrease in carbon dioxid serves, therefore, as an index of the increase of other acids The carbon dioxid tension may be determined directly by examination of the blood or indirectly by analysis of the alveolar air, for in most instances (see above) the tension in the blood and in the alveolar air is approximately the same The simplest and most satisfactory method for the determination of the carbon dioxid tension or the carbon dioxid combining power of the blood is that of Van Slyke ([23]) The technique is easy and accurate results may be obtained very quickly on a few cubic centimeters of blood Perhaps one of the chief advantages of making the determination on the blood itself is that any effort on the part of the patient is obviated and it is not always easy to obtain satisfactory samples of alveolar air from patients who are sick or who cannot cooperate There are various methods for collecting specimens of alveolar air The oldest, and one of the most satisfactory is that of Haldane and Priestley ([24]) in which the subject expires deeply into a long tube and the last part of the expiration is taken for analysis There are certain technical difficulties which cause trouble with untrained subjects, and the fact that many sick patients cannot give a deep enough respiration limits its clinical use It is easier to obtain samples by means of the Plesch Higgins method ([5]), in which the patient rebreathes rather deeply from a rubber bag and the results are quite satisfactory for clinical purposes in spite of the fact that the values are closer to those of the venous than of the arterial carbon dioxid The method devised by Lindhard ([26]) by which multiple small samples are taken at the end of respirations of comparatively normal depth has been used by Boothby and Peabody and with especial success by Debenham and Poulton ([7]) Probably the most accurate method is that recently brought out by Pearce ([8]), but it is not easily applicable to clinical work In all of these methods the samples of alveolar air must be analyzed in some type of special apparatus The apparatus most commonly used is that of Haldane ([27]) and this is undoubtedly the most accurate and satisfactory method but Henderson ([9]) has devised a much simpler and cheaper form that is

quite accurate enough for general clinical purposes Many of the technical difficulties of gas analysis are obviated in the use of the apparatus of Fridericia ([29]) This consists of a special form of glass tube into which the patient expires and the carbon dioxid in the last portion of the expiration is absorbed by adding sodium hydrate directly The volume of carbon dioxid in the expired sample of alveolar air is read on a graduated scale on the tube The method is simple and rapid and the apparatus is well adapted to bedside work but in the obtaining of proper samples of alveolar air one has the same difficulties as in the Haldane method of which it is really a modification

Of less importance than an increase of the H ion concentration of the blood in the production of hyperpnea is a *decrease in oxygen tension* of the arterial blood This however occurs frequently and while it usually depends on a low hemoglobin content it may also be due to an incomplete oxygenation of the blood during its passage through the lungs to a diminished oxygen tension in the inspired air, or to the formation of abnormal hemoglobin compounds The following instances taken from the study of Tompkins Drinker and Brittingham ([30]) on the effect of transfusion on the metabolism in anemia illustrate the degree to which the minute volume rises as the hemoglobin falls

TABLE V

Case No	Hemoglobin per cent.	Metabolism per cent. of Normal	Minute Volume Liters
3	30 90	—11 —14	4 56 4 48
12	40 60	+ 9 — 2	4 50 3 99
14	30 74	+11 —10	5 11 4 19
15	25 95	+15 + 3	6 55 5 51

Another severe case of secondary anemia in which the hemoglobin was 21 per cent (Palmer method) and the oxygen combining capacity was 5 7 volumes per cent (normal about 18 5 volumes per cent) had a minute volume of 9 34 liters The rate of respiration was 13 per minute and the volume per respiration was 720 c c Observations made when testing aviators in the United States Army as to their ability to stand low oxygen tensions in the inspired air show that there is generally some increase in the minute volume when the oxygen has dropped from

the normal of about 21 per cent to percentages of from 16 to 15 per cent Below this there is a slight gradual increase in the respiration down to concentrations of from 12 5 to 9 per cent of oxygen From this point to about 8 5 or 6 per cent oxygen the minute volume increases much more rapidly and at percentages of between 8 and 6 the majority of men examined showed an increase of 5 5 liters over the volume breathed when atmospheric air was being inspired At tensions corresponding to an altitude of 25 000 feet the average minute volume was approximately 14 liters ([31]) As to the effect of incomplete saturation of the blood in patients breathing atmospheric air little is known because comparatively few determinations have been made of the oxygen content of the arterial blood of man in disease It would seem to be quite possible however that in certain conditions such as severe generalized bronchitis there might well be an interference with the proper oxygenation of the blood The presence of marked cyanosis may be an indication of this Pearce ([3]) suggested that the cyanosis in pneumonia is due to the fact that part of the blood flows through a portion of the involved lung and is thus not exposed to the alveolar air Stadie ([33]) has found this to be the case in patients with the influenzal type of broncho pneumonia In normal controls the arterial blood was from 85 to 98 per cent saturated with oxygen and in patients with pneumonia it remained at this level until twelve to twenty-four hours before death when it fell rapidly to as low as 32 per cent This was not associated with any striking diminution in the oxygen combining capacity of the blood The low arterial oxygen seemed to parallel closely the degree of cyanosis Hurter ([0]) who made the first systematic observations on the arterial blood gases in man also found a slight oxygen deficiency in two cases of pneumonia In four cases of heart disease in whom the circulation was compensated the oxygen content of the arterial blood was according to Hurter within the normal limits but in two out of three decompensated cases there was a slight decrease in the oxygen content The cyanosis of congenital heart disease is generally supposed to be due to the arterial blood containing a mixture of oxyhemoglobin and reduced hemoglobin and in this condition the minute volume has been found to be above normal even at rest The increased minute volume in cases of acutely decompensated heart disease with great cyanosis may also be in part due to stimulation of the respiratory center by low oxygen content of the arterial blood In a case of chronic bronchitis and in one of pulmonary tuberculosis Hurter found the oxygen content of the arterial blood to be normal but in another patient with pulmonary tuberculosis and in a patient with a pleural effusion and slight cyanosis the oxygen content was a little below normal Conditions analogous to these are

seen when a part of the hemoglobin is converted into a compound which is not easily dissociable and does not combine with oxygen. This occurs in poisoning by illuminating gas when carbon monoxidehemoglobin is formed and under the various circumstances in which methemoglobin is found. Peabody [34] has described the formation of methemoglobin in the terminal stages of pneumococcus pneumonia and Harrop [3] has found a decrease in the oxygen combining capacity of the blood at the period of collapse in two fatal cases of pneumonia following influenza.

Another type of clinical condition in which marked hyperpnea may arise is that in which there is *increased cerebral pressure* from any cause. In such cases the disturbance of respiration is probably due to pressure on the respiratory center. An extraordinary increase in the minute volume may also be seen in *hysteria*. Paroxysms of intense dyspnea may arise and may persist for remarkably long periods. Sometimes the increase in volume of the individual respiration is the striking feature but more often there is a great increase in rate and the breathing is very shallow. *Observations have been reported on such a case by Peabody* Wearn and Tompkins [86]. The patient was an extremely neurotic soldier who developed a marked hyperpnea when the mask was put on his face to study his basal metabolism. Before the mask was put on his respiratory rate was 36 per minute after the mask was put on the rate reached 102. The minute volume in the first period was 7 86 liters and in the second period it was 11 69 liters. His metabolism was normal and the oxygen consumption was practically the same in the two periods (243 c c in the first period and 233 c c in the second period). It is characteristic of hysterical hyperpnea that it decreases during sleep and when the patient does not know he is being observed.

Various *drugs* produce a hyperpnea. Thus Higgins and Means [87] found a slight increase of the minute volume of air breathed after the administration of atropin and caffein. With atropin the hyperpnea seemed to depend on an increase in metabolism and with caffein on a stimulation of the respiratory center. Adrenalin also causes a rise in minute volume which depends on an increase of metabolism. Tompkins and Wearn [8] found that this increase was much greater in persons who are hypersensitive to the drug and that it depends on a rise in metabolism.

The Vital Capacity of the Lungs

The *vital capacity* of the lungs is the volume of the greatest possible expiration after the deepest possible inspiration. Its measurement is thus an expression of the depth to which the respiration can be increased. In normal breathing at rest the volume of each respiration is only a

small proportion about 10 per cent of the vital capacity but with the very deep breathing which is brought about by severe muscular exercise or in advanced diabetic acidosis each respiration may amount to as much as 30 40 or even 50 per cent of the total vital capacity It is readily seen that anything which decreases the vital capacity of the lungs may interfere with the breathing in that it reduces the reserve of the respiration A normal man, for instance, breathes 400 c c per respiration at the rate of 15 or a minute-volume of 6 0 liters at rest If his vital capacity is 5 000 c c, and if he is able, during exercise to breathe 40 per cent of this (or 2,000 c c) at each respiration, and at a rate of 30 per minute, it will be possible for him to raise his minute volume to 60 0 liters On the other hand if his vital capacity is reduced to 3 000 c c and if he breathes the same percentage of it at the same rate it will only be possible for him to raise his minute volume to 36 0 liters. The vital capacity is thus an important factor in determining the degree to which the minute volume can be raised in the development of hyperpnea

Since 1846 when Hutchinson ([39]) first introduced the use of the spirometer the question of the vital capacity of the lungs in disease has been frequently investigated in medical clinics Much information has been obtained but the value of the determinations has been limited by the difficulties in establishing normal standards for comparison In 1855 Arnold ([40]) published an extensive and carefully compiled monograph in which he showed that age sex height size and expansion of chest and habit of life may all have a considerable effect on the vital capacity of the lungs Attempts have been made to find a simple relationship between vital capacity and some readily obtainable body measurement or a formula which would give a constant for the relation between vital capacity and body size but none that is entirely satisfactory has been found In an attempt to establish normal standards for the vital capacity, Peabody and Wentworth ([41]) studied 140 healthy persons including physicians nurses medical students and a number of ward patients who would be classed as normal from the point of view of the respiration The subjects ranged between 20 and 50 years of age but the majority were between 20 and 30 years They were on the whole a representative group of normal people in every day life Since the vital capacity decreases with advancing years it would have been better if more elderly normal persons had been studied but in spite of this lack the normal standards established appear to be of practical value. It was felt to be important to have as simple a method of standardizing results as possible and after attempting various ways it was found that a classification based on sex and height was practical and sufficiently

accurate In the determination of the normal standards of vital capacity therefore the observations on 140 normal persons were grouped according to sex, and for each sex three subgroups were made on the basis of height The average normal vital capacity was determined for each subgroup Having thus established the normal standards subsequent determinations were referred to these and expressed in percentage of the appropriate normal Ninety six normal males were studied and divided into three groups according to their height Group I included those who were 182 5 cm (6 feet) tall or over, and the normal standard computed was 5 100 c c Group II consisted of men between 173 5 cm (5 feet, 8½ inches) and 182 5 cm (6 feet) tall and the average vital capacity which was 4 800 c c was taken as the normal Group III was comprised of persons whose height was between 173 5 cm (5 feet 8½ inches) and 159 5 cm (5 feet 3 inches) The normal standard of this group was 4 000 c c With one exception the vital capacity in all the males examined varied between 86 and 121 per cent of the normal figure while 84 per cent were within 10 per cent of the normal The largest vital capacity was 7 180 c c, or 141 per cent This was found in a powerful man who had recently been a member of the varsity crew track and football teams in a large university Four other members of this group had a vital capacity of 6 000 c c or over and all had undergone severe athletic training Table VI gives the details of the determinations of vital capacity in the normal males and shows the actual and percentage variations from the standard adopted in each group

TABLE VI

THE VITAL CAPACITY OF THE LUNG OF NORMAL MALES

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity c.c.	Number Within 10 per cent of Normal	Highest Vital Capacity c.c.	Lowest Vital Capacity c.c.	Highest per cent	Lowest per cent	Number Below 90 per cent of Normal
I	14	6+	5 100	9	7 180	5 030	141	99	0
II	44	Over 5 8½" to 6'	4,800	41	5 800	4,300	121	90	0
III	38	5 3" to 5 8½	4 000	31	5 080	3,450	127	86	1

Special attention is called to the last column in Table VI It will be seen from this that only one of the ninety six normal subjects had a vital capacity which was more than 10 per cent below the appropriate

normal standard For practical purposes then, the significant fact is the demonstration that healthy males almost invariably have a vital capacity of 90 per cent or more of the normal standard A decrease in the vital capacity below 90 per cent will therefore suggest some pathological condition

The women were also subdivided into three groups according to their height Group I was composed of those who measured over 167 cm (5 feet, 6 inches) tall, and the vital capacity was 3 275 c c Group II consisted of those who were from 162 cm (5 feet, 4 inches) up to and including 167 cm (5 feet, 6 inches) The normal standard for this group was found to be 3,050 c c Group III was made up of persons from 154 5 cm (5 feet 1 inch) up to and including those who were 162 cm (5 feet, 4 inches) tall The standard vital capacity for this group was 2,825 c c Table VII gives an analysis of variations from the normal standards in the different groups

TABLE VII

THE VITAL CAPACITY OF THE LUNGS OF NORMAL FEMALES

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity c.c.	Number Within 10 per cent of Normal	Highest Vital Capacity c.c.	Lowest Vital Capacity c.c.	Highest per cent	Lowest per cent	Number Below 90 per cent. of Normal
I	10	Over 5 6"	3 275	5	4 075	2 800	124	86	[illegible]
II	13	Over 5 4" to 5 6	3 050	9	3 425	2 660	112	[illegible]	2
III	21	5 4" or less	2 825	16	3 820	2 500	135	89	1

As far as these figures go then one may state fairly definitely that in normal persons the vital capacity is at least 85 per cent and almost always 90 per cent or more of the normal standards adopted for each group In elderly persons a slight decrease from these standards may be expected

Lundsgaard and Van Slyke (42) have attempted to find a more accurate basis for the comparison of measurements of vital capacity in different individuals and they have investigated the relationship between chest volume and vital capacity The chest is considered to be a geometrical figure and the product of the three dimensions length depth and breadth is assumed to represent a volume proportional to the chest volume The height of the chest is taken as the length of the sternum from incisio intraclavicularis to a point just below articu

lar o sterno xiphoidea The depth is then taken as the horizontal distance from the middle of the sternum at the insertion of the third rib to the spinal column and the breadth is the distance between the sixth ribs in the midaxillary line The points between which the measures are taken are almost without any muscular covering The ratio between the vital capacity and chest volume is calculated a $\frac{100 \text{ vital capacity}}{\text{chest volume at rest}}$ and the average ratio is given as 45 A study of a larger series of cases seems to show that this figure is too low In 16 normal cases of Lundsgaard and Van Slyke which could be compared by the two methods 1 was more than 10 per cent below and 3 more than 10 per cent above the normal standard when the relationship to chest volume was used while 2 were more than 10 per cent below and 5 more than 10 per cent above by the standards of Peabody and Wentworth By either method the variations from the normal should probably be considered as at least 10 per cent either way In pathological conditions it is a decrease below the normal that is of especial significance Physical training and deep breathing exercises are important factors in increasing the vital capacity On account of these and other conditions which have already been mentioned as influencing the vital capacity it is not likely that any absolutely accurate means of determining normal standards in a simple way will be found and the variations under different circumstances in a given individual will be of more significance than the variations from any arbitrarily chosen standard

The simplest method of determining the vital capacity is by means of a small well balanced spirometer of about 8 liters capacity such as is illustrated in Fig 1 The subject takes the deepest possible inspiration and then expires completely into the spirometer The volume of the expiration can be read with an accuracy of 50 c c at least from the calibrations on the wheel Difficulty is sometimes experienced in that many persons tend to continue inspiration after having inserted the tube into the mouth It is therefore well to start with the spirometer partly filled with air By means of a short pin which is placed on the wheel at the zero point and a pointer that is easily movable and catches on the pin it is easy to arrange so that even after an inspiration the pointer will give the actual zero point at the beginning of expiration In order to obtain accurate results proper cooperation on the part of the subject is of course necessary and this is sometimes difficult to obtain in sick or very weak persons

It has long been known that the vital capacity of the lungs may be decreased in heart disease and a systematic study of the occurrence

and significance of this decrease was made by Peabody and Wentworth (*loc cit*) As a result of 224 observations on patients with various types of cardiac disease they conclude that there is a close relation between decrease in vital capacity and the tendency to dyspnea Compensated patients who do not complain of dyspnea on exertion have a normal vital capacity Patients with more serious disease in whom dyspnea is a prominent symptom have a low vital capacity, and the decrease in vital capacity runs parallel to the clinical condition Changes in the clinical condition are usually associated with changes in the vital capacity As a patient improves his vital capacity tends to rise and as he becomes worse it tends to fall They find that determinations of

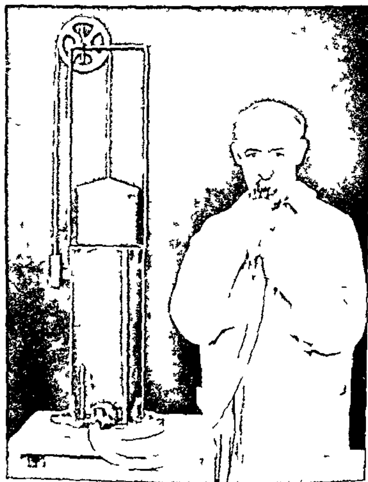


Fig 1—Spirometer for Determination of Vital Capacity of the Lungs

the vital capacity in cases of cardiac disease are often of practical value as they give quantitative information as to the tendency to dyspnea and thus indirectly, as to the clinical condition and the reserve power of the patient. If the vital capacity of patients with heart disease is expressed in terms of the normal standards for sex and height as given above four distinct groups may be recognized in which there is a close relationship between clinical condition and percentage decrease of vital capacity from the normal figure. Among the patients in whom the vital capacity is 90 per cent or more of the normal standard very few complained of symptoms referable to their hearts. Dyspnea was not more prominent in their histories than it would be found to be in a similar group of normal persons. Many of them entered the hospital for other diseases and the cardiac condition was found only in the course of the routine examination. Twenty three out of twenty five were able to work and the majority without much restriction. They were almost invariably in a good state of compensation and if as rarely happened they were prevented from leading a normal life this was usually on account of cardiac pain or some other disturbance. Patients with a vital capacity of 70 to 90 per cent differed from those having a higher vital capacity in that almost all gave a history of dyspnea on moderate exertion and had a distinctly limited cardiac reserve. About half of them were able to do a moderate amount of work. A number of them had had periods of more or less severe cardiac decompensation in which there had been a further drop in the vital capacity. These are therefore to be regarded as border line cases in whom the activities must be somewhat limited but in whom under favorable circumstances there is little evidence of cardiac insufficiency. The third group of cases in whom the vital capacity was from 40 to 70 per cent of the normal was characterized by the fact that all its members were in a much less favorable clinical condition than were those who had a higher vital capacity. Dyspnea on even moderate exertion was always noted in the history and was indeed usually the most prominent symptom complained of. Even within the group there was a fairly definite relation between the vital capacity and the clinical condition. Thus all patients with a vital capacity of from 40 to 45 per cent of the normal were in bed. Some of them were slightly dyspneic even when completely at rest while the others became dyspneic on the least exertion. With a vital capacity of from 45 to 60 per cent of the normal patients were rarely dyspneic while in bed and most of them could walk slowly around the ward without becoming short of breath. A few were living at home and could come to the outdoor department but they all had to walk slowly and avoid stairs or hills. When the vital capacity was between

60 to 70 per cent the patients have usually been able to walk fairly comfortably, many could come to the hospital on foot and could even go upstairs without any special distress Only 7 per cent of the persons in this group were at work when they were examined and in all cases the work done was very light Attacks of severe cardiac decompensation occurred with considerable frequency in this group of patients and the mortality among those who at some time have been members of the group was rather high The fourth group consisted of cardiac patients with a vital capacity which was 40 per cent of the normal or less They were usually bedridden and severely decompensated Many of them had dyspnea even when completely at rest Patients whose vital capacity falls as low as this during their first period of cardiac insufficiency may improve so much that they are able to return to a fairly normal life but the occurrence of such a low vital capacity in later attacks of decompensation makes for a distinctly unfavorable prognosis Few patients who at any time fell into this group showed great clinical improvement, and more than one half had died

Table VIII summarizes these observations on the relation between the vital capacity of the lungs and the clinical condition of patients with heart disease

TABLE VIII

THE RELATION OF THE VITAL CAPACITY OF THE LUNGS TO THE CLINICAL CONDITION IN PATIENTS WITH HEART DISEASE *

Group	Vital Capacity per cent	Number of Cases	Mortality per cent	Symptoms of Decompensation per cent	Working per cent
I	90+	25	0	0	9-
II	70 to 90	41	5	2	54
III	40 to 70	67	17	39	7
IV	Under 40	23	61	100	0

The cause of the decrease of the vital capacity of the lungs in heart disease is somewhat complex as there may be several factors involved each of which can act to limit the movement of the lungs Some of these

* Certain cases were tested several times and owing to changes in vital capacity they appear in more than one group In the "mortality" column they are included only in the lowest group into which they fell "Symptoms of decompensation" indicates dyspnea while at rest in bed or on very slight exertion Under "working" are included only those actually at work and able to continue Many other patients in Group II were able to work but they are not included as they were still in the hospital

affect the movement of the chest wall and prevent a normal expansion of the thoracic cavity Weakness of the intercostal muscles rigidity of the bony framework or ankylosis of the costal joints may act in this way Alterations in the lung tissue itself may cause a diminution in its elasticity as is seen in emphysema Accumulations of fluid in the pleural cavities prevent the normal expansion of the lungs and great cardiac hypertrophy pericardial effusion or mediastinal tumors may produce a similar result The normal inspiratory depression of the diaphragm is interfered with by intrathoracic conditions which make it assume a flattened position even during quiet respiration, and by intra abdominal conditions which push it upward Hepatic enlargement tympanites and ascites are examples of such conditions Fluid within the bronchi and smaller air passages may prevent the entrance of air into considerable portions of the lung That is of course frequently found in the dependent parts of the lungs in severely decompensated patients The effect produced by a generalized bronchitis is not wholly clear from the results which have as yet been accumulated The decrease in vital capacity associated with this condition is frequently much less than one would expect and observations suggest that the intense dyspnea sometimes occurring in cardiac patients who acquire an acute bronchitis is largely dependent on some factor other than a change in the vital capacity

In many cases and particularly in acutely decompensated patients conditions such as those just mentioned appear to account for the decrease in the vital capacity of the lungs in a wholly satisfactory manner In other instances especially where dyspnea is only experienced on moderate exertion all of these factors may be absent and yet the vital capacity may be low enough to explain fully the history of shortness of breath The cause of the low vital capacity in such cases is not absolutely certain but the work of Siebeck ([43]) on the determination of the lung volumes in heart disease bears on the question and suggests that the decrease in vital capacity may be due to an overfilling or engorgement of the pulmonary vessels and a consequent diminution of the elasticity of the lungs If this is proved to be true it would signify that the determinations of vital capacity may give direct evidence as to the state of the pulmonary circulation Such information would be of great value in the study of cardiac insufficiency Other methods of examination bear chiefly on the greater circulation and disturbances in the pulmonary circuit are only recognizable when of sufficient grade to cause the passage of fluid out of the vessels into the air spaces and the production of rales

Similar detailed studies have been made by Carvin Lundsgaard and

Van Slyke ([44]) on 31 men and 20 women with pulmonary tuberculosis The results agreed with former observations in showing that the vital capacity is usually decreased in this disease, and further, that the decrease in vital capacity bears a close relation to the extent of the pathological process Thus in 9 men with incipient pulmonary tuberculosis the average vital capacity was 87 per cent of the normal according to chest volume, and 89 per cent according to the standards for height of Peabody and Wentworth In 13 cases with moderately advanced lesions the vital capacity was 68 per cent of the normal referred to chest volume and 74 per cent if referred to height In 9 patients with severe pulmonary tuberculosis, the average vital capacity was 62 per cent according to the normal standard based on chest volume, and 60 per cent according to the standards for height

There are of course many other pathological conditions in which the movement of the lungs is restricted, and the vital capacity is reduced This is the case for instance in many patients with emphysema with pneumonia, or with pleural effusions

A secondary effect on the respiration, caused by a reduction in the vital capacity of the lungs is the production of an hyperpnea If the vital capacity is considerably decreased the breathing tends to become more rapid and more shallow and the minute volume becomes greater This is due to the fact that the 'dead space" is not decreased in proportion to the respiratory surface A larger part of each respiration thus remains in the dead space and does not come in contact with the respiratory epithelium As a result of this the oxygenation of the blood is maintained by raising the minute volume of air breathed and this is done chiefly at the expense of the rate of respiration The effect of reduction in the vital capacity on the minute-volume is shown by the following observations made on a patient with one side of the chest almost completely filled by pleural effusion before and after tapping

TABLE IX

	Vital Capacity c c	Vital Capacity per cent	Minute Volume Liters	Volume per Respiration c.c.	Rate of Respiration	Metabolism per cent of Normal
Before Thoracentesis	1950	49	8.06	360	22 5	25
After Thoracentesis	2700	68	6.96	503	14 0	18

This effect on the minute volume is however apparently only of definite consequence if the decrease in vital capacity is of a considerable degree Peabody Wentworth and Barker ([45]) in a study of the basal metabolism

and minute volume in patients with heart disease found that if the cases were divided into two groups, depending on whether the vital capacity was above or below 60 per cent of the normal minute volume averaged about 30 per cent higher in the group with the low vital capacity while the basal metabolism only averaged 10 per cent. higher The rate averaged 13 per minute and the volume per respiration 471 c c for the cases with the higher vital capacity while the rate was 22 and the volume per respiration 408 c c. in the cases with low vital capacity

Lung Volumes

In addition to studies on the vital capacity many observations have been made on other measurements of *lung volumes* Those which have received particular attention are the total capacity at full inspiration the residual air, which is left in the lungs on full expiration, the middle capacity or the amount of air in the lungs at a point halfway between normal inspiration and normal expiration the complementary air, which is the difference between the middle capacity and the total capacity and the reserve air, or the difference between middle capacity and residual air

The usual method used for determining these volumes has been by means of the inspiration of a given amount of air containing a known percentage of oxygen or hydrogen and the analysis of it after it has been mixed with the air in the lungs From the dilution which the gas undergoes the volume of the air in the lungs can be calculated Lundsgaard and Van Slyke however in the article quoted above have found from observations on 11 normal men and 7 normal women that there is a numerical relationship between external chest measurements and total capacity middle capacity and residual air By the use of the ratios thus established the lung capacities normal for a chest of given measurements can be estimated

In *emphysema* Siebeck ([45]) Bohr ([46]) and Bittorf and Forschbach ([47]) all found an increase in the residual air an increase in the middle capacity and a decrease in the reserve air The complementary air may be normal increased or decreased according to Bittorf and Forschbach but the vital capacity is characteristically decreased In *pulmonary tuberculosis* Garvin Lundsgaard and Van Slyke (*loc cit*) state that the total capacity and middle capacity are normal in incipient cases but that the residual air may be increased In moderate and in advanced cases they agree with Siebeck in that the total capacity is decreased the middle capacity is decreased or may be normal while the residual air is normal or sometimes increased Siebeck says the residual air is increased in proportion to the total capacity In pleurisy

Van Slyke ([44]) on 31 men and 20 women with pulmonary tuberculosis. The results agreed with former observations in showing that the vital capacity is usually decreased in this disease, and further, that the decrease in vital capacity bears a close relation to the extent of the pathological process. Thus in 9 men with incipient pulmonary tuberculosis the average vital capacity was 87 per cent. of the normal according to chest volume and 89 per cent. according to the standards for height of Peabody and Wentworth. In 13 cases with moderately advanced lesions the vital capacity was 68 per cent. of the normal referred to chest volume and 74 per cent. if referred to height. In 9 patients with severe pulmonary tuberculosis, the average vital capacity was 62 per cent. according to the normal standard based on chest volume, and 60 per cent. according to the standards for height.

There are, of course, many other pathological conditions in which the movement of the lungs is restricted and the vital capacity is reduced. This is the case, for instance, in many patients with emphysema, with pneumonia, or with pleural effusions.

A secondary effect on the respiration, caused by a reduction in the vital capacity of the lungs, is the production of an hyperpnea. If the vital capacity is considerably decreased, the breathing tends to become more rapid and more shallow, and the minute-volume becomes greater. This is due to the fact that the "dead space" is not decreased in proportion to the respiratory surface. A larger part of each respiration thus remains in the dead space and does not come in contact with the respiratory epithelium. As a result of this the oxygenation of the blood is maintained by raising the minute volume of air breathed and this is done chiefly at the expense of the rate of respiration. The effect of reduction in the vital capacity on the minute volume is shown by the following observations made on a patient with one side of the chest almost completely filled by pleural effusion before and after tapping.

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This effect on the minute volume is, however, apparently only of definite consequence if the decrease in vital capacity is of a considerable degree. Peabody, Wentworth and Barker ([45]) in a study of the basal metabolism

in the size of the individual breaths the onset being marked by shallow respiration the middle by respirations of greater volume and the termination again by shallow breathing This is, however not a constant feature and the beginning of the period of breathing may be marked by deep respirations Cheyne Stokes respiration is not in itself a pathological phenomenon as it is frequently seen in normal persons during sleep—particularly in infants and in old persons and in hibernating animals It may also occur normally in people at high altitudes Under pathological circumstances it is not at all infrequent and it arises in many different conditions Among the more common conditions with which it is associated are cerebral lesions accompanied by increased intracranial pressure arteriosclerosis uremia myocardial insufficiency lesions of the aortic valve morphine poisoning and profound stupor arising from various other causes Cheyne Stokes respiration is perhaps most often seen in patients with diseases of the circulatory system and in them it forms a very characteristic clinical picture Sometimes it persists both by day and by night, but usually it disappears in the daytime recurring in the evening, and it is very frequently the cause of what is generally referred to as nocturnal dyspnea The usual story is that just as the patient is dozing off to sleep he is wakened by a severe paroxysm of dyspnea which makes him sit up straight in bed gasping for breath After a short period of distress he falls asleep again only to be awakened by another attack of dyspnea following which he once more goes to sleep until after a short interval he is aroused again by a period of labored breathing If pneumographic tracings are taken it will be found that Cheyne Stokes respiration is present and that the patient is dozing off in the periods of apnea and awakening in the periods of respiration This condition is sometimes called cardiac asthma but the term is singularly inappropriate as the characteristic feature is the apneic pause which is of course not a part of the true asthmatic attack In the milder cases anything which rouses the patient such as the entering into conversation will occasionally make the periodicity of respiration become less marked or even disappear

Cheyne Stokes breathing is accompanied by phasic variations in the blood pressure and many investigations have been made on the relation of the changes in blood pressure to the changes in respiration Barbour ([30]) says 'All theories of periodic respiration which do not take into account periodic circulatory interference have yet to explain why the breathing does not remain rhythmical ' Cushing ([31]) first showed in experiments on dogs that the blood pressure tends to keep higher than the intracranial tension and that an increase in the latter brings about a rise in the former The changes of blood pressure associated with

with effusion Siebeck and Bittorf and Forschbach state that the reserve air is decreased and the complementary air may also be decreased This results in a low vital capacity and a low total capacity The middle capacity is decreased but is about normal in its percentage relation to the total capacity, and the residual air is usually decreased

Investigations by Rubow ([48]) and by Bittorf and Forschbach show that in heart disease the residual air is approximately normal in volume The low vital capacity is due essentially to a diminution in the reserve air, but the complementary air may also be decreased Most observations indicate that the middle capacity in heart disease is normal or somewhat decreased but that it is increased in its percentage relationship to the total capacity

Clinical interest in the determination of the lung volumes in disease was largely stimulated by the work of Bohr (*loc cit*) who laid great stress on the importance of the middle capacity According to the teaching of this eminent Danish physiologist an increase of the middle capacity in emphysema is a useful compensatory change by means of which the circulation through the lungs is facilitated and the same explanation was applied to the increase in the middle capacity in exercise Rubow believed that the relative increase of the middle capacity in heart disease was similarly a mechanism by which the pulmonary circulation is aided and the ventilation of the lungs increased He even went so far as to ascribe the dyspnea in certain cases to the muscular exertion necessary to raise the middle capacity At the present time however there seems to be a general doubt as to the physiological and pathological significance of variations in the middle capacity Changes in the residual air are undoubtedly of importance A decrease probably indicates a diminution of the respiratory surface An increase means that each inspiration is less effective in altering the composition of the alveolar air This condition is seen in emphysema in which as has been shown by Hoover ([49]), the subject is put to a further disadvantage by the fact that the dead space is also increased

Irregularity of Respiration

Apart from the slight irregularity of rate and depth of breathing that occurs with more or less constancy in normal persons even when at rest the most important type of respiratory arrhythmia is the periodic form known as Cheyne Stokes respiration This type of breathing consists essentially of alternating periods of complete apnea and of grouped respirations The apneic phase is commonly shorter than the respiratory phase and the latter is usually characterized by a waxing and waning

to this classification that not all of the cases of Cheyne Stokes breathing will fit readily into the two groups but that these two groups as originally described by Eyster probably embrace most of the cases and that the exceptions are likely to be isolated instances In experiments on cats under the influence of morphin Barbour was able to demonstrate that both of these types of Cheyne Stokes respiration may occur In both groups in those in which respiration is accompanied by rise of blood pressure as well as in those in which apnea is accompanied by rise of blood pressure he believes that the variations in blood pressure are the essential cause of the periodic breathing The apparent paradox that rises of blood pressure may produce exactly opposite effects is explained by the fact that they may supply the medulla with blood of different constitution In the cardiac type ' he considers that the respiratory center is greatly depressed by some cause such as morphin edema of the brain uremia or circulatory insufficiency Because of this the center does not respond normally and a period of apnea results which may persist so long that asphyxia of the heart with a fall of blood pressure and a slowing of the pulse rate results This leads to an anemia of the respiratory center but in spite of its depression the latter 'responds to the double stimulus of anemia and CO_2 by a eries of respirations These relieve the cardiac asphyxia and thus improve the medullary circulation and the CO_2 tension is reduced Both respiratory stimuli being thus eliminated the condition of apnea recurs In the type of Cheyne Stokes respiration described by Eyster as occurring in association with increased intracranial pressure and called by Barbour the vasomotor type the latter holds that the heart is less affected and the waves in the blood pressure arise from periodic stimulation of the vasomotor center by asphyxial products The respiratory center whose excitability to these products has been reduced to about the level at which the vasomotor center responds to them shows parallel periodicity' Observations have been made by Pembrey and Allen ([56]) on the composition of the alveolar air during the changes in the respiration in Cheyne Stokes breathing At the onset of respiration following apnea the carbon dioxid is high and the oxygen low At the end of the period of respiration the percentage of carbon dioxid in the alveolar air falls and the oxygen rises They believe that the essential feature in producing the periodicity of the respiration is a decrease of the excitability of the respiratory center Only when the combined stimulus of increasing carbon dioxid and decreasing oxygen has reached a certain level does the center respond and then it reacts so extensively that it reduces the stimulus below the threshold and apnea follows Similar observations were made by Douglas and Haldane ([57]) in artificially

increased intracranial tension cause alternating periods of blood flow and anemia in the brain, and simultaneously with these there may occur phasic variations of the breathing, in such a way that the periods of high blood pressure and blood-flow in the brain are accompanied by respiration, while the periods of low blood pressure and anemia are accompanied by apnea. Eyster ([52]) continued this work experimentally and amplified the results by the study of clinical cases with increased intracranial pressure in whom he found the same relationship between the changes of blood pressure and the alternating periods of respiration and apnea The intervals of apnea are accounted for by the fact that the excitability of the respiratory center is reduced by the anemia, and the increase in the stimulus to respiration which develops during apnea is not as great proportionally as the decrease in the excitability The vasomotor center is stimulated to greater activity during the periods of anemia It thus raises the blood pressure increases the flow of blood to the medulla and by this means raises the excitability of the respiratory center so that finally the latter responds to the abnormally high stimulus and respiration begins The increased supply of well aerated blood then causes the vasomotor center to relax A fall of blood pressure results, and with this an anemia which decreases the excitability of the respiratory center below the threshold of the stimulus, so that respiration ceases and the period of apnea begins In a second group of clinical patients, in whom Cheyne-Stokes respiration was associated with cardiovascular or renal disease, Eyster found an almost exactly reversed relationship between the blood pressure changes and the phases of respiration In these cases the blood pressure began to fall at about the middle of apnea and continued to fall until the third or fourth respiration when it began to rise again, increasing through the rest of the respiratory period and reaching its maximum at approximately the middle of the succeeding interval of apnea In both types of cases the increase of blood pressure was accompanied by a rise of pulse rate and the fall of blood pressure by a slowing of the pulse The same relationship between blood pressure and respiration was found by Pollock ([53]) in a similar series of cases, and by Clark and Hamill ([54]) in four cases including one of severe opium poisoning In the latter there was a prolongation of the a v interval in addition to the slowing of the pulse and fall of blood pressure during apnea Fulton ([55]) has reported a case in which Cheyne-Stokes respiration was associated with auricular flutter There was a rise of blood pressure during apnea and an increase of pulse from approximately 45 during the period of dyspnea to 80 during apnea Fulton cites cases from the literature that do not fall definitely into either of these two groups and concludes with regard

variation in the rate and depth of breathing the irregular occurrence of periods of apnea of varying duration and by frequent deep sighing respirations It is particularly associated with meningitis Conner and Stillman ([11]) found it to be present in 27 per cent of 43 cases of meningitis its incidence among the adults and non tuberculous cases being greater than among the children and tuberculous cases In the same group Cheyne-Stokes respiration was observed in 53 per cent of the cases The latter occurs in so many clinical conditions that it is of course of very little diagnostic significance but as the result of the study of a large series of pneumographic records on adults and children Conner and Stillman believe that Biot s breathing is almost pathognomonic of meningitis

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produced Cheyne Stokes respiration in man, but they lay especial emphasis on the effect of oxygen want It was found that the respiratory center responded when the carbon dioxid tension was below normal and this is explained by the suggestion that the low oxygen tension leads to the formation of lactic acid in the respiratory center, and that this augments the carbon dioxid in its effect as the stimulus to the respiration When the respiratory phase begins the lactic acid is oxidized and the carbon dioxid removed so that the respiratory stimulus becomes greatly reduced and a period of apnea follows White and his associates ([58]) found in a clinical case of prolonged Cheyne-Stokes breathing that the H ion concentration of the blood was abnormally high at the onset of dyspnea but about normal at the beginning of apnea They argue from this that the excitability of the respiratory center was depressed since it did not respond to a stimulus of normal intensity It is of course very difficult to disprove the theory of Douglas and Haldane of a local formation of abnormal acid in the respiratory center, but observations reported by Peabody ([19]) on the carbon dioxid tension of the blood show that there was no general acidosis of severe grade and that in the individual case there was no significant fall in the carbon dioxid tension with the onset of periodic dyspnea That want of oxygen may be a factor of importance in the production of Cheyne Stokes respiration is also indicated by the reports of Pembrey and Beddard and French ([59]), of Pembrey ([60]), and of White and his co workers ([58]), who showed that the periods of apnea may be made to disappear if oxygen in high concentration is given to the patient to breathe The same result may be brought about if the stimulus to respiration is increased by raising the concentration of carbon dioxid in the inspired air It is however of interest in this connection to note a fact that is very striking when one is attempting to study the respiration of patients with Cheyne Stokes breathing This is that even the application of a mask and valves through which the subject can breathe a wholly adequate amount of atmospheric air may suffice to cause the cessation of the periodicity of respiration in the less marked cases The tendency of patients who have mild degrees of Cheyne Stokes breathing to assume a regular normal rhythm as the result of being roused by almost any nervous stimulus is wholly in accord with what is generally accepted as the underlying feature of periodic respiration Whatever disagreement there may be as to the details of the physiology of Cheyne Stokes breathing most authors are in harmony in believing that it is fundamentally dependent on a decreased excitability of the respiratory center

Somewhat similar to Cheyne Stokes breathing is the respiratory arrhythmia known as Biot s breathing This is characterized by constant

CHAPTER X

VITAMINS AND VITAMIN DEFICIENCIES

By TOM D. SPIES and HUGH R. BUTT

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INTRODUCTION

The advances in nutrition have received a great deal of publicity in the lay and scientific press during the last few years probably because of the most unusual and dramatic circumstances of the discovery of the vitamins Many of the reports are correct but others are not reliable Consumers are being subjected to a ballyhoo that brings to mind stories of the Indian tonic days Vitamins have been reported to cure almost every illness of man or beast The modern science of nutrition although it may seem to some to promise miracles offers no elixir of life and no panaceas It does offer specific therapy for vitamin deficiency diseases and holds promise for far reaching results in the near future Certain it is that vitamins are necessary for the health and vigor of the higher forms of life yet it is equally certain that they are of no value where no deficiency exists They are organic food substances which in small quantities are necessary for maintaining proper growth and continued health of the human body The amounts required are so small that it is almost certain that they act as catalysts or help to form such in the human body They are important in the biochemical systems of the body which govern the oxidation of carbohydrates proteins and fats They have functional relationships with minerals and perhaps with all other essential elements of the dietary

Already vitamins are used widely in medicine By prescribing them judiciously many physicians apply them successfully in their practice of medicine Others use them injudiciously and with no success Some refuse to use them at all Still others prescribe them for appearance sake The physician has been justifiably sceptical toward the introduction of each new vitamin as a therapeutic agent but sometimes he has let his doubts give way to an attitude of complete confidence a confidence

and the practice of medicine will be enriched by a full realization that the deficiency diseases occur as complexities rather than as single entities and must be treated as such Convalescence from nutritional deficiency diseases often is shortened greatly by administering vitamins in suitable mixtures rather than by administering a single vitamin

The use of vitamins in medicine illustrates vividly the immense surge that can be given to the biological or chemical field when it progresses to the point where it has important clinical application Because of its great scientific and therapeutic value research on the vitamins has been of intense interest to the authors of this chapter In writing these sections on the vitamins we have looked backward over a large experience and have eliminated all but those facts that seem essential to the physician who would achieve his goal of full rehabilitation of every patient with nutritional deficiency diseases It is our hope that most of the material in this chapter will be of immediate value in the practice of medicine and that much of it will interest the biochemist the biologist the physiologist the pharmacologist and the student of nutrition

In the following pages we will discuss the vitamins in which the practicing physician will be particularly interested the four fat soluble vitamins A D E and K the four water soluble vitamins C (ascorbic acid) and B (thiamin nicotinic acid amide and riboflavin) and folic acid Each of the sections has been written as a separate unit concerned only with one of these vitamins and its corresponding disease Theories have been discussed as little as possible and all the material is presented with as little prejudice as strong personal opinions allow

VITAMINS A

Epidemics of xerophthalmia and keratomalacia had been reported in the medical literature some thirty or forty years before the compound termed fat soluble A' was recognized These conditions were observed to appear chiefly among children even at an early date a dietary origin was suspected and cod liver oil was noted to be effective in ameliorating the conditions These clinical obervations then were followed by many experimental studies results of which suggested strongly that there was present in certain foodstuffs a fat soluble compound which was essential for normal growth It was not however until 1913 that McCollum and Davis reported the occurrence in certain foods of a compound termed fat soluble A In 19 2 it was shown clearly that the

not always warranted The rapidity with which these advances in nutrition have come, which is shown in Fig 1, is almost unparalleled in medicine and there is great need for investigation by conservative physicians, who will test each new material and appraise its effect on human beings under controlled conditions

That the present state of our knowledge of nutrition frequently is confusing and often contradictory is due largely to inadequately controlled clinical investigations in a field that once was considered very simple Clinical experimentation with the vitamins must continue, and at the same time we must exercise great scepticism in regard to what may be attributed to their therapeutic effect

THIAMIN
VITAMIN K
NICOTINIC ACID
VITAMIN E
RIBOFLAVIN
VITAMIN D
VITAMIN B COMPLEX
ASCORBIC ACID
VITAMIN A
FAT SOLUBLE
WATER SOLUBLE
VITAMINS

Fig 1 Diagram showing important vitamins with important dates in their development

As physicians we abhor "polypharmacy" yet there is a logical basis for including sufficient amounts of a variety of vitamins in a single therapeutic preparation The vitamins tend to occur together in nature

the substance readily absorbs oxygen in solution and is markedly pro-oxygenic when undergoing oxidation. However highly oxidized vitamin A has no biological activity. Vitamin A is very sensitive to oxidation and auto-oxidizes readily. It is heat stable but of course insoluble in water. Vitamin A does not show any absorption band in the visible region of the spectrum but it does show a rather broad absorptive region in the ultraviolet. These properties form the basis for the spectrophotometric method for the quantitative estimation of vitamin A.

On the basis of recent reports it appears that there exists in addition to vitamin A compound designated as 'vitamin A_2.' In chemical structure vitamin A_2 is related very closely to vitamin A_1 and biologically the activity is the same. Rather extensive investigations of the distribution of these two forms of vitamin A have led definitely to the conclusion that vitamin A_1 predominates in the tissues of salt water fishes and that vitamin A_2 predominates in the tissues of fresh water fishes. The absence of vitamin A_2 *from the liver of mammals* and other land animals probably can be explained by the absence of vitamin A_2 from their food. Vitamin A_2 has not been isolated in pure crystalline form. There is no evidence that vitamin A_2 plays any significant role in mammalian nutrition.

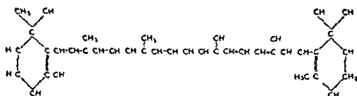


Fig 3 The structural formula for beta carotene

There are many reasons for assuming that some other types of vitamin A exist. Recently[8] a geometric isomer of vitamin A_1 has been reported which has biological potency nearly the same in kind and magnitude as that of vitamin A_1.

Most of the vitamin A available to man in his diet is in the form of its precursors, the yellow and red carotenoid pigments provitamins. For this reason the chemical properties of these compounds are rather important. There are nine different naturally occurring compounds known as provitamins A[9]. These are alpha, beta and gamma carotene, cryptoxanthene, echinenone, myxoxanthin, leprotene, aphanin and aphanicin. These provitamins A belong chemically to a special class called 'carotenoids'. They are extremely sensitive to oxidation, auto-oxidation and

anti-ophthalmic factor in cod liver oil could be destroyed by oxidation without destruction of the anti-rachitic factor

In these early experiments it was noted that swelling of the lids of one eye or both eyes developed in animals, rats, subsisting on a diet deficient in vitamin A, after which there commonly developed an inflamed and catarrhal condition of the conjunctiva with a bloody or purulent discharge It was noted that, if this ophthalmic condition was not treated and the animals continued to live, the cornea became affected, and blindness resulted Significantly it was noted also that without any local treatment, if the ophthalmic disease was not too far advanced the symptoms disappeared rapidly after the ingestion of food containing an adequate amount of vitamin A This relationship of diseases of the eye to dietary deficiency also was demonstrated experimentally in other species as well as rats and it was shown also in these studies that certain diseases of the eye of man might be the result of deficiency of Vitamin A Soon it was reported that xerophthalmia in man could be prevented or cured by the administration of food rich in the A vitamin[1]

Chemistry

Although between 1913 and 1915 McCollum and Davis and Osborne and Mendel had ascertained the presence of fat-soluble A in cod liver oil and in butter it was not until 1933 that Karrer synthesized perhydro vitamin A The structural formula of vitamin A is shown in Fig 2

Fig The structural formula of vitamin A

This primary alcoholic structure of vitamin A is important in that it allows for esterification and, therefore the formation of compounds of vitamin A with protein bile acids and fatty acids These compounds of vitamin A are decomposed with liberation of the vitamin by such hydrolytic processes as occur in saponification, the vitamin is an alcohol hence it is not itself saponifiable Vitamin A is a hydrogen acceptor probably because of its unsaturated form There is some evidence to indicate that

Absorption of the vitamin reaches the maximum in three to five hours after administration Although there apparently is some loss of vitamin A in the stool nothing is known of the degree of destruction of vitamin A in the gastrointestinal tract under either normal or pathological conditions Studies on a person who had a fistula of the thoracic duct after the administration of vitamin A or carotene by mouth revealed that very little of the carotene passes through the chylous fluid whereas nearly all of the vitamin A can be recovered

Carotene is absorbed less readily than vitamin A, and absorption itself is subject to several more hazards Proper absorption of carotene requires the presence of bile in the intestinal tract and in those conditions in which bile is completely or partially excluded from the intestinal tract or in those instances in which bile salts of good quality are excreted poorly bile must be given as a supplement to insure proper absorption Chronic diarrhea pancreatic dysfunction celiac disease or sprue also may inhibit the absorption of carotene As with vitamin A a certain amount of normal absorption of fat also seems necessary for proper transportation of carotene across the intestinal wall It has been shown, further that mineral oil may inhibit seriously the absorption of carotene For this reason mineral oil should not be given soon after meals Absorption of carotene reaches a maximal level in the blood in from 7 to 8 hours after administration and the amount excreted in the feces accounts for only a small portion of the unutilized excess The rest of it apparently finds other channels of excretion or is destroyed in the intestine or elsewhere The kidney apparently does not play any part in the disposition of either vitamin A or its precursors, unless the body is flooded with either carotene or vitamin A

The capacity to store vitamin A varies widely among different species of animals The rat has a remarkable capacity for the storage of vitamin A whereas the rabbit and guinea pig retain little of this substance even when they subsist on diets rich in carotene In these particular animals a large part of the total content of vitamin A in the body is present in the liver although small amounts appear in the lungs and kidneys However in other animals for instance fish greater amounts of vitamin A are deposited in the tunica propria of the mucosa of the intestine than in the liver

After absorption a greater portion of the carotene is held in the liver where it gradually disappears from the Kupffer cells as the concentration of vitamin A in the liver increases Vitamin A itself also is stored properly in the liver in the Kupffer cells In human beings the vitamin A

light but are stable to heat Little is known of the biogenesis of provitamins A, and none have yet been synthesized Of this large group of pigments, however, the beta form yields two molecules of the vitamin whereas each of the other produces only one molecule This can be seen easily in the formula of beta carotene shown in Fig 3 Theoretically, if the splitting ocurrs in the middle, one molecule may give rise to two molecules of vitamin A It was the ingenious research of Karrer which first proved that beta carotene contains two beta ionone rings It was shown also by these investigations that the beta-ionone ring is an essential component of the molecular structure of vitamin A All the carotenoids that yield vitamin A exhibit characteristic absorption bands in the visible region of the spectrum

Although its exact function is unknown, carotene obviously is of great importance in the physiological processes of plants It constitutes a family associated closely with chlorophyll, although it is not lost when the chlorophyll disappears at the time of the yellowing of leaves However, it is destroyed completely in dry dead leaves Rapid drying by artificial heat also destroys the provitamin All these facts are important because carotene of green leaves is brought indirectly into human nutrition through milk and eggs

The conversion of the precursors into vitamin A apparently takes place in the animal liver, and it is of clinical significance that this transformation is retarded in the presence of phosphorus poisoning and in other forms of hepatic injury It is thought that the conversion of carotene into vitamin A takes place by the aid of an enzyme in the liver called "carotenase" Although there is much evidence that the liver is the site of conversion, there is also some evidence that the human pancreas is involved[7]

Physiology

The absorption and utilization of vitamin A and carotene depend on many factors and because of the differences in absorption and utilization of these two compounds, both of them must be described

Vitamin A is a fat soluble compound, and its absorption apparently is facilitated greatly by the simultaneous absorption of a certain amount of fat Most observers believe that the presence of bile is not necessary for proper absorption of vitamin A, although it is still perhaps good therapeutic medicine to administer bile salts with concentrates of vitamin A in the treatment of patients who have obstruction of the biliary tract

content in the milk of the lactating human subject in the same way as in the cow Doses of 100 000 I U daily more than doubled the vitamin A content of the milk [12]

Food Sources

Vitamin A occurs only in the animal organism Fish liver oils are the richest source of vitamin A Milk (3 U S P units per gram) butter (50 U S P units per gram) and egg yolks all are rich sources of vitamin A of animal origin Margarine when fortified with vitamin A can be substituted for butter in the ordinary diet[13] Vitamin A is fairly stable to heat and not appreciably soluble in water, it is however destroyed by oxidation and foods which are heated for long periods show an appreciable loss of vitamin A potency Since the vitamin activity is not affected at the temperature of boiling water foods cooked in this manner retain their vitamin A potency Canned foods have practically the same vitamin A value as the corresponding fresh foods and foods which are stored in the frozen state maintain their maximal vitamin A value but dried and dehydrated foods show considerable loss of vitamin A content

The provitamins A occur in plants and generally are absent from the animal organism There are however a few exceptions Almost pure betacarotene has been found in the corpus luteum in the human placenta and in the adrenal gland

Human beings depend almost entirely on provitamins for their source of vitamin A Fortunately vitamin A is widespread in nature in the form of the precursors the yellow and red carotenoid pigments These pigments are found in the plant world being distributed from bacteria to garden fruits and vegetables The pigments are found chiefly in association with chlorophyll and in the green leaves of plants but this is not invariably true since carrots and sweet potatoes with their yellow color also are rich in these substances

Apparently there is a direct parallel between greenness (chlorophyll content) and vitamin A activity in foods of plant origin Among the best sources of vitamin A are thin green leaves The exact relationship between the degree of greenness and vitamin A activity is not understood but it is well known that the outer green leaves of iceberg lettuce or cabbage are much more potent in vitamin A than are the inner leaves Peas green beans green peppers parsley stocks asparagus and green celery all are known to have a high content of vitamin A Carrots sweet potatoes apricots yellow peaches and yellow tomatoes all of which

content, as in all animals, is much lower in the liver at birth than in the liver of the normal adult irrespective of the diet of the mother The liver probably stores about 95 per cent of the vitamin A reserve of the body and the amount stored is, as a rule, smallest in the liver during childhood and increases gradually with advance in age Examination of the livers of healthy persons, who died suddenly from accidental causes, shows them to average 331 U S P units of vitamin A per gram of liver tissue

The exact mechanism by which vitamin A is called forth from its reserve stores is not known, but from several sources it appears that the distribution of vitamin A in the circulating blood and tissues is controlled in part by the nervous system Evidence has been presented to indicate the existence of compounds of carotene and vitamin A with protein, probably albumin[8]

The excretion of vitamin A appears to be highly selective Neither vitamin A nor the provitamins are excreted by the kidneys unless the organism is given an excessive dose of these substances It has been reported[9], however that in human urine vitamin A is absent in health but present in association with some pathological conditions particularly pneumonia and chronic nephritis

Using fluorescence microscopy as a method of visualization of vitamin A in tissue cells, Steigmann and Popper[10] found that the concentration of vitamin A in the human liver varies even under normal conditions Among young infants there was very little storage but in the embryo of about five months development considerable amounts appeared although these depots of vitamin were reduced later, and at birth only traces were distinct The human adrenal tissue and lactating breast tissue were found to be rich in vitamin A, but the normal tissues of the human kidney brain, cornea bronchi and urinary tract and the inactive breast were found to be free of the vitamin It is interesting that by this method it was found that the retinas of rats dying of avitaminosis A with ulceration of the cornea contained vitamin A[11]

Only extremely small quantities of these compounds can be found in the feces and it is assumed for this reason that unutilized excesses find other channels of excretion or are destroyed in the intestine or elsewhere

Human milk contains both carotene and vitamin A The colostrum from the human breast has from two to three times the biological vitamin A activity of early milk and early human milk has from five to ten times the biological vitamin A activity of cow s milk The administration of vitamin A in large doses effectively increases the vitamin A

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possess a yellowish color, are rich sources of vitamin A Nuts and cereal grains, with the exception of those having considerable green and yellow color, are very poor sources of vitamin A Yellow corn is the most important vitamin A food in this group

Experimental Pathological Physiology

The observations of Wolbach and Bessey, Mellanby, and Moore have established growth of bone and the nature of such growth is important aspects of vitamin A deficiency Wolbach and Bessey consider that deficiency of vitamin A retards bone growth but Mellanby, on the contrary, believes that lack of the vitamin leads to increased activity of both the osteoblasts and osteoclasts of the bone with proliferation of cancellous bone at the expense of compact bone[14, 1, 16] Formerly it was believed that vitamin A produced a profound effect on the nervous system Wolbach and Bessey[14], however, have shown that in deficiency of vitamin A in rats skeletal growth is retarded earlier than that of the soft tissues in general including growth of the central nervous system, and that in the white rat at least the nervous manifestations are due to pressure effects caused by relative overgrowth of the central nervous system

Epithelium — No definite changes in the skin of experimental animals have been described as following deficiency of vitamin A

Relationship to Infection — Since McCollum in 1917 first pointed out that severe spontaneous infection develops in rats suffering from deficiency of vitamin A, there has been a bulk of literature on this subject and for many years it was believed that vitamin A did aid in some manner in combating the tendency toward infection in man It is believed by some that the frequency of occurrence and high fatality rate of pneumonia in infants, who suffer from deficiency of vitamin A, result from disturbance of function of the mucosa of all parts of the lung Others believe that the provision of vitamin A in large amounts is beneficial in preventing the common cold but this whole subject is in general very controversial Undoubtedly severe deficiency of vitamin A in man will lower the resistance to infection, yet administration of vitamin A during the course of an infection apparently does not have any beneficial effect on the outcome of the infection unless a severe deficiency of vitamin A also is present Certainly there is enough evidence to indicate that there are many other factors which have an influence on infection equal to that of vitamin A and that some factors have a greater influence

Hence, there is no justification for calling vitamin A the anti infective vitamin

Eye — Decreased facility for adaptation to dark is one of the earliest functional changes associated with deficiency of vitamin A. Evidence has been reported which suggests that the visual purple of the retina is a conjugated protein in which vitamin A is a prosthetic group. Exposure of the retina to light leads to a chemical change with bleaching of the visual purple and before sensitivity can be restored the pigment must be reconstructed. This process perhaps is reversible but it is not always efficient and therefore direct supplies of vitamin A must be constantly available. The selection of color and other visual functions depend on light of high intensity associated with the cones of the retina whereas the rods are sensitive only to light and are especially adapted to function in dim light. Visual purple is found only in the rods and apparently serves to transform the energy of dim light into nerve impulses which within limits vary according to intensity of the light. Although it was believed formerly that the cone played no part in the metabolism of vitamin A it has been demonstrated recently that the formation of visual violet or iodopsin in the cone takes place in much the same manner as does formation of visual purple in the rods. In the experimental animal as in man pathological changes in the eye occur late. Changes in both animals and man are essentially the same. Metaplasia of the epithelium of the conjunctiva and cornea is the earliest change followed by vascularization of the cornea with edema and perhaps necrosis. Accumulation of keratin itself favors infection of the cornea which may lead ultimately to ulceration and hypopyon keratitis

Liver — It has been well established that the liver enacts a major role in the metabolism of vitamin A but the exact manner in which this is accomplished is still unknown. As early as 1895 Hori had made the clinical observation that night blindness and keratomalacia frequently accompany disease of the liver. Later it was shown that in patients who have alcoholic cirrhosis without jaundice there are subnormal powers of adaptation to darkness which improve on the adequate administration of vitamin A. Others have demonstrated repeatedly that the content of vitamin A in the liver and blood of patients who have severe hepatic injury nearly always is decreased markedly

Low values for vitamin A in the blood have been reported to be associated with severe hepatic damage. Clinical improvement was accompanied by the gradual return to normal of the content of vitamin A in the blood[17]

possess a yellowish color, are rich sources of vitamin A. Nuts and cereal grains, with the exception of those having considerable green and yellow color, are very poor sources of vitamin A. Yellow corn is the most important vitamin A food in this group.

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There is little evidence to show that dermatological conditions are influenced by, or influence the content of vitamin A of the plasma [9]

In the skin vitamin A apparently is concerned with the process of keratinization In conditions of long standing deficiency of vitamin A the skin becomes dry and hyperkeratotic These changes are evident



Fig 4 Cutaneous manifestations of vitamin A deficiency (Frazier C N Hu Chuan Kuei and Chu Fu Tang Arch Dermat and Syph 1943 XLVIII 1)

microscopically as follicular hyperkeratosis parakeratosis and dyskeratosis Steffens as reported by him and his associates [1] eliminated vitamin A from his diet for a period of 6 months and although his capacity for adaptation to dark remained within normal limits his skin became dry and there were microscopic changes in the skin similar to those just mentioned

Human Requirements

Vitamin A is essential to normal metabolism. Although the exact minimal requirement of vitamin A for man still is unknown, considerable work has been carried out in an effort to settle this point. Since the recommended daily allowances for definite nutrients as defined by the Food and Nutrition Board of the National Research Council and later adopted by the Council on Foods and Nutrition of the American Medical Association represents the thoughts of the leaders in these particular fields, it would seem well that these should be accepted.

For the average man and woman who weighs 70 and 56 kg respectively, the daily allowance is 5,000 international units. In the latter half of pregnancy 6,000 international units are required, and during lactation the requirement is 8,000 international units. For children aged less than a year 1,500 units are required, for those aged one year to three years [illegible],000, for those four to six years old, [illegible],500, for those seven to nine years old, 3,500, and for those ten to twelve years old, 4,500. For children more than twelve but not more than fifteen years of age 5,000 units are required, and for those sixteen to twenty years of age 6,000 units. Allowances in all these instances may be less if the substance provided is vitamin A, and greater if it is chiefly the provitamin carotene.

Deficiency of Vitamin A in Man

Apparently deficiency of vitamin A in man is not common in this country. Normal subjects placed on a diet deficient in vitamin A appear to have sufficient stores to maintain vitamin A in the blood and tissues such as the retina at an adequate level for many months. Many investigators have established that deficiency of vitamin A is an uncommon disturbance even among the ill and poorly nourished.[18, 19] However, follicular hyperkeratosis, pityriasis rubra pilaris and cirrhosis of the liver all are diseases in which the thresholds of adaptation to dark have been found to be abnormal and in which these thresholds have been improved materially through the administration of vitamin A.

Epithelium. — Cutaneous lesions (Figs. 4, 5, 6 and 7) associated with deficiency of vitamin A and analogous to those occurring in other epithelial structures have been reported by several investigators. The skin contains, however, no appreciable vitamin A in spite of the fact that the vitamin has an important influence on cutaneous and structural growth.

Eye — In the United States xerophthalmia keratomalacia and nyctalopia caused by deficiency of vitamin A are rare The early pathological changes are the same as those described previously for animals Xerophthalmia is most common in infancy although it may be seen at all ages

The loss of visual acuity in dim light is one of the first symptoms of deficiency of vitamin A in man Definite pathological changes in the eye however occur late in man when diets deficient in vitamin A are employed[1] Night blindness usually develops in adult persons before any



Fig 6 Pityriasis rubra pilaris demonstrating keratoderma palmaris (By courtesy of Department of Dermatology Mayo Clinic)

types of ophthalmia develop but usually the disease is ushered in by small triangular white patches which appear on the outer and inner sides of the cornea covered by white foamlike spots consisting of corneal epithelium which has been shed and accumulates in this position Bitot's spots Photophobia and conjunctivitis appear early followed by light brown pigmentation of the conjunctiva The keratinization of the conjunctiva may extend to the cornea and lead to extreme softness and degeneration of the cornea and to ulceration perforation and total destruction of the eye keratomalacia This disease may destroy the eye rapidly and its prompt recognition therefore is very important

The severe dermatoses of deficiency of vitamin A are found in the same geographical distribution as the advanced ocular manifestations. The lesions consist of epidermal hyperplasia and glandular atrophy and are represented by papular eruptions around the pilosebaceous follicles.



Fig. 5. Pityriasis rubra pilaris demonstrating follicular hyperkeratosis. (By courtesy of Department of Dermatology, Mayo Clinic.)

These usually occur among persons between the ages of 16 and 30 years and not among infants. The condition is common among men and nearly all who have the dermatosis also have obvious ocular manifestations of deficiency of vitamin A. Reports from the East indicate that the incidence of this symptom is as high as or higher than that of the ocular symptoms.[3]

is satisfactory for measuring deficiency of vitamin A Others contend that although some relationship exists between readings of the biophotometer and the status of nutrition of vitamin A yet the relationship is not close enough to warrant use of the test as a means of diagnosis of subclinical deficiency of vitamin A It has been pointed out that the method is time consuming and that for this reason alone its routine clinical use practically is ruled out Certainly minor fluctuations in adaptation to dark in terms of deficiency of vitamin A should receive little emphasis unless physical methods are used to test the reliability of the differences It is true that a majority of workers believe that the study of adaptation to dark can be used as a test for deficiency of vitamin A but until differences in technic and in interpretation of results have been resolved it is impossible to be certain how far recorded observations represent physiological facts In fact by having human beings subsist on a diet deficient in vitamin A over long periods some investigators have been unable to produce clinical night blindness or even changes in adaptation to dark.[27] It may be as stated by Josephs[4] that all this discrepancy is the result of lack of knowledge of methods for determining storage of vitamin A Certainly at present there is no single simple formula for computing the needs of the body for vitamin A Measurements of dark adaptation provide only one approach to the subject

No definite correlation between biophotometer readings and the content of vitamin A in the blood has been observed Although it has been demonstrated that the amount of vitamin A in the blood is dependent on the amount provided in the diet yet evidence as to whether determination of vitamin A in the blood is of value in judging the nutritional status still is contradictory Recently evidence has been presented which suggests that the concentration of vitamin A in the blood plasma is a considerably more sensitive indicator of deficiency of vitamin A than is the test for adaptation to dark

The same contradictory evidence is presented for the measurement of vitamin A by examination of scrapings from the eye and vagina On the basis of results of all of these studies it would be judged that the methods for measuring deficiency of vitamin A of man still are somewhat unreliable and demand further study Among some physicists and chemists there still is doubt as to whether the small quantities of vitamin A present in the blood stream of man can be measured with the chemical methods available

For a number of years Spies and associates have studied the ocular symptoms occurring as a result of malnutrition among human beings. Asche and Spies have observed that Bitot s spots frequently are observed among these patients, and that they disappear soon after large doses of vitamin A have been administered Follicular conjunctivitis is observed frequently, particularly among children, and it also often disappears after



Fig. / Pityriasis rubra pilaris demonstrating keratoderma plantaris (By courtesy of Department of Dermatology Mayo Clinic)

the administration of large amounts of vitamin A Mild conjunctival xerosis also has been attributed to deficiency of vitamin A [1 6]

Methods for Measuring Deficiency of Vitamin A

The fact that night blindness is an early symptom of deficiency of vitamin A led to the development of visual adaptation in dim light as a method for the diagnosis of deficiency of this vitamin Whether deficiency of vitamin A can be measured by testing adaptation to dark continues to be a most controversial subject Some contend that this method

Lesions of the Skin — Within the past few years several groups of investigators have reported on patients who had cutaneous lesions which were considered to be the result of a deficiency of vitamin A These lesions are shown best in Figs 4 5, 6 and 7 Many investigators believe that this manifestation of deficiency of vitamin A is overlooked frequently

Subclinical Form —It is practically impossible to clinically diagnose subclinical deficiency of vitamin A These forms probably are frequent however, and must be considered under various conditions in which inability to carry out proper absorption or proper intake or utilization of vitamin A is suspected

Differential Diagnosis

Although various laboratory procedures such as measurement of the content of vitamin A in the blood and testing for adaptation to dark in time may be very helpful in diagnosis of deficiency of vitamin A the best method of differential diagnosis still depends on close clinical observation Night blindness xerophthalmia and keratomalacia are not confused easily with any other conditions and should be recognized readily Treatment should be instituted at once

Treatment of Vitamin A Deficiency

The use of vitamin A in treatment is indicated in those syndromes which result from deficiency of vitamin A in the diet or from deficiency of vitamin A resulting from improper absorption or utilization The best treatment with vitamin A still involves prophylactic therapy In general the response to treatment with vitamin A of specific syndromes resulting from the deficiency is slow and recovery may involve weeks and months of time

Persons who possess normal powers of absorption of carotene and vitamin A and who have night blindness may be treated by diet alone or diet *plus vitamin A supplement In those cases in which night blindness results from faulty* absorption such as is caused by gastrocolic fistula gastrointestinal continuity first must be re established before treatment unless the compounds are administered intramuscularly

Xerophthalmia and keratomalacia require the same treatment as night blindness but it is perhaps wise to administer doses of from 50 000 to

Toxicity

If large amounts of vegetables containing carotene are ingested by normal persons and persons suffering from certain diseases such as diabetes, carotene may accumulate in the skin in amounts sufficient to cause a deep yellow color Such a condition is known as carotenemia This condition, so far as is known, is compatible with good health

It is difficult to evaluate the reports concerning the injurious effects on man which follow the ingestion of cod liver oil Some observers when administering large doses, 80 c c, of cod liver oil, have noticed the appearance of dermatitis of the face and scalp Sensitivity to cod liver oil resulting in eczema also has been reported However, on the basis of the general favorable clinical results of the use of cod liver oil and other preparations containing vitamin A the physician should be extremely certain that it is harmful before he discontinues its use Certainly, when the average therapeutic dose is employed, no such toxic effect will be observed

It has been reported recently that in growing rats given the purest available form of vitamin A in excess, skeletal fractures and hemorrhage develop rather characteristically

Diagnosis of Vitamin A Deficiency

Undoubtedly the incidence of marked deficiency of vitamin A in the United States is very small Of course the supposition that states of partial deficiency may be common has received repeated emphasis but as yet no definite methods have been developed by which these subnutritional states can be diagnosed

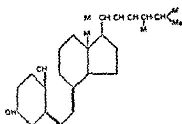
Night Blindness — The first symptom of this syndrome is loss of visual acuity in dim light This particular symptom may occur in the presence of various diseases of the eye such as toxic amblyopia, detachment of the retina or retinitis pigmentosa, but these conditions usually are excluded easily The patient may complain of dancing lights before his eyes or similar visual disturbances and of course, by means of testing for adaptation to dark he will exhibit a pathological condition This condition must be suspected in cirrhosis of the liver, instances of severe and prolonged pyloric obstruction severe chronic diarrhea and any other condition which may produce a generalized nutritional deficiency

Xerophthalmia — The symptoms of xerophthalmia have been given already under the heading 'Deficiency of Vitamin A in Man—*Eye*"

VITAMINS D

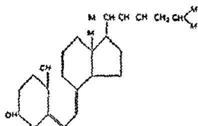
There is little doubt that rickets has been prevalent for many centuries It was not however until about 188 that cod liver oil was suggested as a remedy for the condition[9] Hopkins[10] suggested that rickets was caused by the absence of an accessory foodstuff and in 1913 the beneficial influence of sunlight on the assimilation of calcium was reported

It was Mellanby[11] however who in 1918 discovered the nutritional importance of animal fats in the normal calcification of bones and who concluded that the antirachitic factor was similar in distribution to fat-soluble A Later rickets was induced in rats by special diet and Steenbock and Black[3] as well as Hess[12] found that antirachitic potency could be induced in foods by ultraviolet irradiation McCollum named the antirachitic material vitamin D



Calciferol (Vitamin D)

Fig 8



Activated 7 dehydrocholesterol (Vitamin D)

Fig 9

Fig 8 The structural formula for calciferol (vitamin D)
Fig 9 The structural formula for activated dehydrocholesterol (vitamin D)

CHEMISTRY

A compound which can be activated to a vitamin D is known as a provitamin D These compounds belong to the sterol family and are distributed widely over the animal and plant kingdoms The most prevalent provitamin D in higher animals and in human beings is 7 dehydrocholesterol whereas ergosterol is predominant in yeast molds and plants Activated ergosterol viosterol or calciferol is known as vitamin D (Fig 8) and activated 7 dehydrocholesterol is known as vitamin D_3 (Fig 9) There is no vitamin D_1 this term having been used for a lumisterol calciferol mixture originally mistaken for a pure vitamin Vitamin D_4' is the term sometimes applied to activated 22 dihydroergosterol and vitamin D sometimes is referred to as 7 dehydrositosterol

100 000 units in the form of potent fish liver oil by the oral or parenteral route

In the presence of lesions of the skin the best results have been obtained from doses of 100,000 to 300 000 international units of vitamin A administered daily over a period of two to three months It must be remembered that results of treatment of lesions of the skin require periods of to 3 months, and the physician should not become discouraged because there is not a dramatic response

When patients who have chronic diarrhea are being treated, it should be borne in mind that these patients require more vitamin A than is necessary for normal persons Patients, who have hepatic disease likewise require rather large doses of the vitamin In such instances from 10 000 to 20 000 international units of vitamin A administered daily is considered to be an adequate dose A person, from whose intestinal tract bile is excluded completely or partially, should be given supplements of bile salts with vitamin A supplement

Obviously in the treatment of any of these conditions diets rich in vitamin A and its precursors should be prescribed in addition to the potent supplement containing vitamin A

the absorption of the liposoluble vitamins The factor of absorption also enters into such diseases as celiac disease sprue and other fatty diarrheas which are attended commonly by deficiency of vitamin D

From the intestines vitamin D is said to be absorbed into the blood There is also some evidence to show that most of the vitamin D is absorbed first into the lymph of the thoracic duct and that its rate of absorption is comparable to that of vitamin A[31] Normal human blood contains about 50 to 1.5 international units per 100 c c of serum The human being apparently has no special place for storage of vitamin D although substantial amounts can be found in organs such as the liver spleen brain and lungs The heart has been found consistently to be devoid of any stored amounts of vitamin D Failure of this storage mechanism coupled with defective secretion of bile salts may lead to secondary avitaminosis D in cases of hepatobiliary disease This possibility has been emphasized further by the observation that in animals normal hepatic function is necessary to promote the antirachitic action of vitamins

Apparently vitamin D can pass only in limited amounts through the placental walls New born babies have practically no vitamin D in their tissues even though their mothers had an abundant supply during gestation Recent data clearly indicate that the ability to increase the vitamin D content of human milk or cow s milk by large oral doses of vitamin D is very limited Even when massive doses were ingested daily by a mother the antirachitic potency of the milk was insufficient completely to prevent rickets in the breast fed infant[5]

No results of quantitative studies are available which would indicate how much destruction of vitamin D occurs in the organism Obviously some is destroyed and some is excreted mainly through the bile and intestinal tract but not through the kidneys

The concentration of vitamin D in the blood of human beings has been studied inadequately Observations indicate that there is a wide zone of so called normal concentration varying from 66 to 165 U S P units per 100 c c of blood

Calcium and Phosphorus Metabolism — Vitamin D is concerned chiefly with the regulation of calcium and phosphorus in the body but the exact chemical nature of this mechanism is not understood clearly No one yet has demonstrated whether vitamin D enters directly into the combination with these elements or their salts or merely assumes the role of catalyst However it can be demonstrated easily that the growth of bones is related to the action of vitamin D An early symptom of defi

Ergosterol has the empirical formula $C_{28}H_{44}O$ The conversion of this provitamin to vitamin D is not a simple process but involves a series of photochemical changes which are initiated when ergosterol is exposed to ultraviolet light During this reaction several substances are formed lumisterol protachysterol tachysterol and finally, calciferol (vitamin D_2) Further irradiation of vitamin D_2 produces a toxic compound which has no antirachitic activity and is known as "toxisterol"

Inactive 7 dehydrocholesterol is the principal provitamin occurring with the cholesterol of animal fat Ultraviolet irradiation of the skin feathers and fur of animals, therefore, produces activated 7 dehydrocholesterol For this reason the principal antirachitic agent present in natural fat oils, eggs and irradiated milk is activated 7 dehydrocholesterol Just as in the case of ergosterol the changes produced by the activation of 7 dehydrocholesterol are entirely photochemical The physical and chemical properties of 7-dehydrocholesterol resemble those of calciferol Both of these substances have been isolated in crystallin form but attempts at synthesis have been unsuccessful

Dihydro-tachysterol is a sterol of considerable practical importance It is prepared from the acid ester of tachysterol and when administered to human beings causes an increase of the concentration of calcium in the blood In therapeutic circles it is known as "A T 10", and it is useful in infantile and postoperative hypoparathyroid tetany

The isolation and identification of the pure vitamins D have been most difficult tasks The exact number of naturally occurring vitamins D is unknown, but only four vitamins designated D_2 D_3 D_4 and D have been prepared in essentially pure form Only vitamin D_2 and vitamin D_3 have been isolated in the pure form from fish liver oils These vitamins are fat soluble, and in the pure state are white, odorless crystals Vitamin D_2 (Fig 8) is an isomer of ergosterol from which it is derived and it has the empirical formula $C_{28}H_{44}O$ Vitamin D_3 (Fig 9) can be derived from 7 dehydrocholesterol

Physiology

Absorption and Storage — The various forms of vitamin D are absorbed readily from the intestinal tract and especially from the small bowel This absorption is facilitated by the presence of fat but bile salts also are necessary for proper absorption Recent investigations indicate that the salts of desoxycholic acid may be concerned particularly with

especially resorptive ones in which osteoblastic activity is increased the concentration of phosphatase in the serum is increased Such is the case in rickets An increase in the concentration of phosphatase in the serum is perhaps the first definite evidence of development of the rachitic condition it precedes roentgenological changes and diminution of the amount of serum phosphate The concentration of serum phosphatase is high in cases of active rickets and the administration of vitamin D decreases the concentration toward normal but more slowly than it decreases the concentration of calcium and phosphorus The concentration of phosphatase may not reach normal for several months after there is evidence of healing The increase of the concentration of serum phosphatase in cases of rickets apparently acts as a protective mechanism

The difference in action between vitamin D and parathyroid extract is often the source of confusion and it is important to the clinician that this distinction be clear Although both preparations increase the concentrations of calcium and phosphorus in the serum parathyroid extract acts specifically on the serum calcium and in parathyroid tetany it may even decrease the concentration of serum phosphate In cases of rickets the principal action of vitamin D is in raising the low concentration of serum phosphate only when administered in very large doses does it raise the concentration of serum calcium to more than normal Parathyroid extract increases the concentration of serum calcium by withdrawing the element from the bone vitamin D exerts this effect by increasing the intestinal absorption of calcium or by diminishing its re excretion from the intestinal mucosa The distinction may be clearer if the reader remembers that the toxic effect of parathyroid extract is decalcification but that that of vitamin D is hypercalcification

Although the parathyroid glands have been shown to undergo hypertrophy in cases of rickets this is a result rather than the cause of rickets Indeed injections of parathyroid extract have been shown to retard the healing of rickets and removal of the parathyroid glands from animals makes the production of rickets more difficult

Food Sources

Vitamin D occurs in nature only in small amounts Only in small quantities likewise does it occur in most members of the animal kingdom The living plant and fresh vegetables contain no detectable amount of this vitamin

Although the fat from fish contains relatively large amounts of vita

ciency of vitamin D is a lowered content of phosphorus in the blood serum and later, a lowering of the blood level of calcium

In general the concentrations of calcium and phosphorus in the blood serum reflect the amounts of these elements ingested The ratio of these elements seems to be important in the rachitogenic diet, since a high calcium and low-phosphorus diet is associated with a low content of inorganic phosphate in the blood serum and vice versa The absolute amount as well as the ratio determines the content of calcium and phosphorus in the body fluids and these values increase as the amounts given are increased However in the presence of an adequate amount of vitamin D the values for calcium and phosphorus in the serum tend to become normal regardless of the type of diet employed

Although secondary in importance to the calcium phosphorus ratio the acid base ratio of the diet may be a factor in the production of rickets or tetany There is some evidence to show that rickets is associated with an acid metabolism and tetany with an alkaline one In neither of these conditions whether it occurs clinically or is produced experimentally in animals is there a definite alteration of the acid base equilibrium of the blood

The action of vitamin D on calcium and phosphorus metabolism seems to be concerned chiefly with the absorption of the elements from the intestinal tract The normal infant excretes about 90 per cent of his calcium intake in the feces and usually excretes a small amount in the urine When vitamin D is not given the calcium in the urine disappears This is an attempt on the part of the body at conservation of minerals The concentration of calcium in the feces increases and the retention of calcium becomes subnormal If the intake of calcium is low or the deficiency severe the fecal calcium actually may exceed the intake and thus the condition known as "negative calcium balance" ensues A similar sequence of events occurs in the case of phosphorus except that the amount of phosphate contained in the urine usually is increased[16]

The effect of vitamin D in producing a reversal of these conditions is striking The intestinal excretion of calcium and phosphorus is decreased calcium appears in the urine and the calcium balance is restored to normal The changes in the concentration of calcium and phosphorus in the serum are reflectors of this calcium balance

In recent years it has been shown that there exists in the body an enzyme phosphatase which is intimately related to phosphorus metabolism The exact function of phosphatase in the serum is not known but whatever it may be, there is no question that in diseases of the bone and

vitamin D content of viosterol is 100 times that of standard cod liver oil Viosterol owes its vitamin D activity to activated ergosterol

Viosterol in oil is tasteless which obviates the difficulty of administration encountered in the case of cod liver oil Viosterol suffers one disadvantage as compared with cod liver oil and other fish oils that is it does not contain vitamin A However its tastelessness makes it one of the best vehicles for administering vitamin D to adults and older children

Irradiated vitamin D milk is also a source of vitamin D Vitamin D activity is added to milk of this type by exposure to active ultraviolet rays from artificial sources The irradiation is accomplished in such a manner that standardization is fixed at 135 international units per quart It has been found impracticable to irradiate the milk further because of the production of an unpleasant taste In irradiated milk the vitamin occurs chiefly in the form of activated 7 dehydrocholesterol

The various sources of vitamin D vary in potency but may be substituted for each other on the basis of unitage Much work has been done to determine whether there is any difference in the antirachitic activity of the various chemical forms of vitamin D The only conclusion that has been reached at present is that there is no essential difference

In spite of the numerous claims for various preparations of vitamin D in oil cod liver oil is still the most economical form in which to obtain the vitamin Cod liver oil or one of the concentrated fish oils seems preferable to the preparations containing viosterol if for no other reason than that it seems advisable to prescribe a preparation of vitamin D which is also rich in vitamin A rather than one which contains only vitamin D

Experimental Pathological Physiology

According to Wolbach and Bessey[38] experimental rickets in animals duplicates completely the spontaneous disease in man and in animals To understand better the changes in bone which occur in a deficiency of vitamin D the normal sequence in the growth of bones must be understood Long bones increase in length by the endochondral formation of bone The narrow place of epiphyseal cartilage is supported by bone on the epiphyseal surface and its diaphyseal side is penetrated uniformly by capillaries During growth continuous proliferation of cartilage cells occurs on the epiphyseal side and there is degeneration of matured cells on the diaphyseal surface These degenerating cells are replaced by capillaries and osteoblasts, which effect the deposition of bony matrix

min D, the fat of other animals contains little or none of it A very small amount of the vitamin is present in milk and milk products and in the yolk of hen s eggs Sardines, tuna, herring and salmon, either fresh or canned are fairly good sources of the vitamin The average diet, however, contains relatively small amounts of vitamin D

The accepted standard unit for expressing the strength of vitamin D as adopted by the League of Nations Health Organisation and by the United States Pharmacopoeia is defined as "The vitamin D activity of 1 mgm of the international standard solution of irradiated ergosterol found equal to 0 025 micrograms of crystalline vitamin D" This is the international unit (I U) accepted as the U S P unit In administering antirachitic agents the physician should think in terms of units of vitamin D, since this is the only way in which the doses of the various substances containing vitamin D which differ greatly in volume, can be reduced to a common denominator For example, 1 teaspoonful, 4 c c, of cod liver oil contains approximately 350 units, 1 quart of reinforced milk, 400 units and 1 mgm of calciferol, 400 000 units

The most satisfactory sources of vitamin D are fish liver oils. The vitamin D in cod liver oil probably is chiefly activated 7-dehydrocholesterol Cod liver oil is universally obtainable and is effective in the prevention and treatment of any deficiency of vitamin D There is great variation in the concentration of vitamins A and D in the oils obtained from different species of fish The oil of the *Percomorphi* exhibits the greatest concentration of vitamin D Fish oils are prepared by the manufacturer by combining oils from various species in such a way that the final mixture has a concentration of vitamin D equal to that of viosterol in oil These preparations have the merit of providing vitamins D and A in high concentrations, so that both can be administered in doses measured in drops The disadvantage of unpleasant taste is again encountered but the quantity required is small, so that the disagreeable taste is not a serious disadvantage Vitamin D in these preparations has chiefly the form of activated 7-dehydrocholesterol

According to the United States Pharmacopoeia cod liver oil must contain at least 100 units of vitamin D per gram When large dosage of vitamin D is required, more concentrated sources of vitamin D usually are employed One gram of viosterol in oil contains 'at least 10 000 units of vitamin A' to meet the requirements of the United States Pharmacopoeia twelfth revision The special dropper accompanying commercial preparations is designed to deliver a drop containing 222 units The

deformities of the lower extremities from the bending of the bones in children who have assumed the erect posture (Fig 10) Growth of the long bones particularly the femur may be greatly delayed and the adult may be of short stature as a result The epiphyses are enlarged and it is not uncommon for genu valgum or genu varum to develop Occasional instances of dwarfism have a rachitic basis Deformities of the spinal column are not common

In late rickets the changes are similar to those of early rickets except that the osteoid tissue develops in the subperiosteal and endosteal portions rather than at the epiphysis Osteomalacia presents a similar picture

The effect of vitamin D in reversing these changes has been demonstrated clearly with experimental animals After it has been administered the cartilage cells generally appear along the diaphyseal border at the end of 24 hours and extensive vascular penetration is visible within 48 hours this permits the deposition of bone forming salts The mass of irregular cartilage cells becomes arranged into short orderly columns of a few cells and osteoid material is no longer formed This is the basis of the line test as used in assay of vitamin D

It must be remembered that the fundamental defect in rickets is not in the bone It has been shown that slices of rachitic bone and cartilage become calcified when placed in normal blood serum The primary fault in rickets resides in the body fluids which do not make bone salts available to the bone The action of vitamin D is to bring about alteration of the calcium and phosphorus in the body fluids so that they may be available to the bone It has been suggested recently that vitamin D probably does not exert its therapeutic effects through improvement in intestinal absorption of phosphorus but rather by intensification of phosphorus turnover in bone This results in hyperphosphatemia and a decreased visceral phosphorus turnover[4]

Human Requirement

The exact human requirements for vitamin D are unknown The requirement of vitamin D varies greatly among individuals and among persons of various ages Since the average diet furnishes so little vitamin D it must be assumed either that the requirement of vitamin D for man is extremely low or that his needs usually are provided by exposure to sunshine The requirement of vitamin D during adult life has not been determined but undoubtedly the vitamin is necessary for older children and for adult persons The minimal amounts recommended for infants

Wolbach said that the growth of bone by endochondral formation of bone is achieved by a continuously retreating gap in the continuity of tissues maintained on the epiphyseal side by continuous renewal of cartilage cells and on the diaphyseal side repaired by vascular outgrowth comparable to repair of any defect of tissues by the process of organization or granulation tissue formation In normal growth there presents on the diaphyseal side of the marrow cartilage a continuous layer of clear or empty cartilage cells forming an almost straight line"

The cessation of the formation of osteoblasts is the first sign of deficiency of vitamin D in the bone The growth of the cartilage however continues The epiphyseal cartilage increases in width because of continued proliferative activity and this thickening is irregular since the cessation of degeneration does not occur simultaneously in all portions of the plate In the absence of the ingrowth of capillaries and osteoblasts there is a failure of calcification of the cartilaginous matrix and newly formed bones during the active stage of the disease have an osteoid structure The basic structural alteration in rickets is not the failure of formation of bone but the failure of calcification

The disturbance manifests itself most markedly where the most rapid growth occurs for example at the lower epiphysis of the femur Longitudinal sections of a rachitic bone will reveal a wide irregular zone of ossification at the junction of the epiphysis and diaphysis This region is known as the "rachitic zone" Microscopically a large amount of osteoid tissue is found adjacent to the shaft, and irregular columns of cartilage cells project into this osteoid tissue Growth of the bone is delayed or stopped completely in proportion to the severity of the process On microscopic examination of sections of the shaft osteoid lamellae are found under the periosteum and lining the haversian canals and marrow spaces The structural changes in the bone are not identical in every case In one type of the disease there is a large medullary cavity with a thin porous cortex a form approaching osteomalacia In another type the cortex is thick but porous and the medullary cavity is small

The bony deformities resulting from these alterations vary according to the amount of stress to which the individual bones are subjected Before the infant walks there may be flattening of the occiput resulting from the weight of the head since the excess of osteoid tissue in the occipitoparietal bones makes them soft and yielding craniotabes There is enlargement of the costochondral junctions rickety rosary and alterations in the bony thorax may give rise to various deformities Harrison's groove, pigeon breast, funnel breast The weight of the body produces

Some adult persons treated with large doses of vitamin D may complain of nausea headache diarrhea anorexia urinary frequency or lassitude Adults treated with large doses of vitamin D for arthritis have exhibited various manifestations of toxicity the susceptibility of an individual will vary at different times[66a] Danowski and his associates[67] have reported two instances of dangerous complications resulting from the promiscuous and protracted treatment of arthritis with large quantities of vitamin D without medical supervision The patients concerned took from 150 000 to 500 000 international units daily for 6 years in one case



Fig 10 Florid rickets in young twins (*a*) and (*b*) illustrating deformities wide irregular epiphyseal lines and characteristic cupping of the metaphyses (By courtesy of Department of Pediatrics Mayo Clinic)

and for 13 months in the other Both patients experienced osteoporosis anemia elevated values for blood nonprotein nitrogen hypercalcemia and albuminuria Extensive deposits of calcium in the soft tissue developed in one patient One had hypertension with retinal vascular changes *After the administration of vitamin D had been discontinued there was gradual clinical improvement in these two patients However no serious* toxic effects have been reported in cases in which doses up to 1 000 000 units have been administered to rachitic children

In spite of the aforementioned possible effects the physician need

should be sufficient for those of this age group. During pregnancy and lactation and for children less than a year old 400 to 800 international units of vitamin D constitute the daily requirement as recommended by the Food and Nutrition Board of the National Research Council. In administering antirachitic agents, as emphasized previously in this chapter, the physician should think in terms of units of vitamin D since this is the only way in which the doses of the various substances containing vitamin D, which differ greatly in volume, can be reduced to a common denominator.

Methods for Measurement of Vitamin D

When almost pure, crystalline vitamin D is used, it can be determined by measurement of the characteristic absorption spectrum in the ultraviolet. There is no chemical method by which the presence or amount of vitamins D can be determined accurately. Two methods generally are employed for the biological assay of vitamin D. A simple and convenient method[10] which concerns the growth response of chicks has been described recently.

Clinically, roentgenological examination of the bones of the forearm and wrist is recommended both for the diagnosis of rickets and for determining the healing process. Determination of the amounts of calcium and phosphorus in the blood also may be helpful in following the course of rickets in human beings. According to some recent reports phosphatase activity is a valuable and probably the most sensitive index of active rickets.[41]

Toxicity

When extremely large doses of vitamin D are administered to animal or man, certain pathological changes are noted.[1, 42] Hypervitaminosis D is an exaggerated form of the physiological effect of the vitamin. The concentration of calcium and phosphorus in the serum is increased, and calcification occurs at an increased rate. Metastatic calcification may occur in the renal tubules, heart, blood vessels, bronchi and stomach.[4] In advanced degrees of hypervitaminosis D resorption of bone is the most prominent feature.[4] The animals lose weight rapidly, an intense diarrhea develops and death occurs in 5 to 14 days. If smaller doses are administered, the animal may survive and the described lesions will remain for at least 6 months. Diets low in calcium and phosphorus may prevent the calcification process, but the degenerative changes occur

ically In the former there are no apparent symptoms and the hyper-irritability of the nervous system must be elicited by artificial excitation of the peripheral nerves The *manifest form gives rise to tonic states and* generalized convulsions

The most reliable and delicate sign in the diagnosis of latent tetany is Erb s phenomenon A galvanic current is employed to distinguish irri-

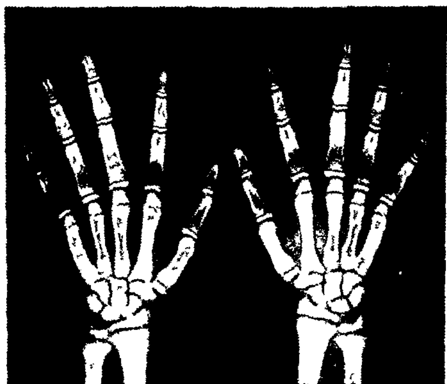


Fig 11 Late rickets in a thirteen year-old child both hands showing the deformities wide irregular epiphyseal lines and characteristic cupping (By courtesy of Department of Pediatrics Mayo Clinic)

tability of the nervous system The Chvostek sign is another rather reliable method of diagnosis The Trousseau phenomenon is described often as diagnostic of infantile tetany *but it probably is not so reliable* as the other two mentioned *Among laboratory observations the presence* of a low concentration of serum calcium is of extreme importance in the diagnosis of tetany In latent tetany the value for the serum calcium

not in general fear toxicity as an effect of vitamin D If renal insufficiency exists, the physician should use caution, repeated urinalyses should be conducted while vitamin D therapy is being employed

Diagnosis of Vitamin D Deficiency

Although some report that the incidence of undiagnosed rickets in certain sections of the United States may be as high as 75 per cent yet the presence of this disease is extremely difficult to determine with reasonable certainty except when the condition is severe Several recent reports tend to affirm this fact[10] The clinical diagnosis hinges on the finding of the various deformities described in the consideration of the pathological changes Among the more important of these are craniotabes and the rachitic rosary In the early or mild stage the physician may encounter difficulty in distinguishing this condition from the normal softness of the baby's skull The rachitic rosary is one of the most constant signs of rickets but much skill is required to distinguish it from the normal enlargement of the costochondral junction An enlarged fontanelle may be evidence of rickets but in many cases there is premature closure Bowlegs (Fig 10*a* and *b*) and deformities of the thorax chicken breast and funnel breast Harrison's groove are of common occurrence but their presence alone is not pathognomonic, since they occur also in many other conditions

To one acquainted with the intricacies of this sort of diagnosis the roentgenogram offers invaluable aid in the recognition of rickets but there are many pitfalls in differential diagnosis A description of the changes revealed by the roentgenogram (Fig 11) is out of place here, the reader can find them in textbooks of radiology Since rickets is not primarily a disease of bone roentgenological evidence may be lacking early in the course of the disease

The concentration of calcium and phosphorus in the serum usually is altered in the presence of rickets The concentration of inorganic phosphate is more constantly lower than that of calcium, the product of the concentration of these two minerals is of more constant value In the acute stage of deficiency of vitamin D there is an elevation in serum phosphatase With few exceptions this appears to be a satisfactory measure for the detection of early acute rickets[20]

Rachitic tetany also is a derangement in calcium and phosphorus metabolism which results from deficiency of vitamin D The latent and manifest forms are the two types of infantile tetany encountered clin

Treatment of Vitamin D Deficiency

Of primary importance in the treatment of rickets is the promotion of healing of the lesion as rapidly as possible The dose suggested as a preventive although it is actually capable of effecting cure in simple

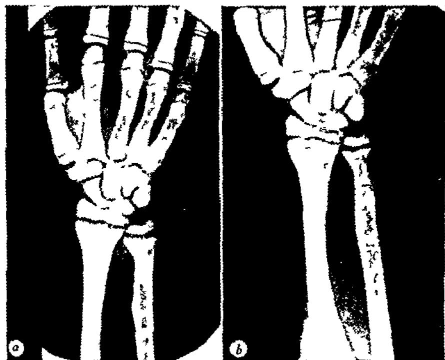


Fig 1 Late rickets in a thirteen year-old child On the left (*a*) before treatment with approximately 1,000 000 units of vitamin D daily in the form of activated ergosterol (The activated ergosterol is not on the market but was used experimentally It was supplied by the Mead Johnson and Company) (*b*) after treatment some five months later (By courtesy of *Department of Pediatrics Mayo Clinic*)

rickets brings about this cure too slowly A dose of 1 000 U S P units 3 teaspoonfuls of cod liver oil daily will control advanced rickets in most cases in 3 to 4 weeks For premature infants often it is necessary to administer 10 000 to 20 000 U S P units daily to effect a cure and the condition of some infants is so refractory to treatment as to require 60 000 units daily Once the disturbance has been brought under control as evidenced by determinations of blood calcium and phosphorus or by

usually is in the neighborhood of 7 to 8 mgm per 100 cc and it may decrease to 5 to 6 mgm in cases of manifest tetany

The outstanding manifestations of tetany are the typical carpopedal spasms the characteristic "tetany facies", laryngospasm and of course the convulsive seizures The diagnosis of manifest rachitic tetany is as a rule, not difficult In the differential diagnosis the physician must consider laryngitis congenital laryngeal stridor, nervous holding of the breath and meningitis

In osteomalacia as in rickets the essential abnormality is deficient calcification of the osteoid tissue It is seen occasionally in men but is encountered most often in women especially among those who are pregnant Usually numerous causative factors are operative in any single case of osteomalacia, but in all cases there is presumably a deficiency of vitamin D In most cases osteomalacia as observed in the United States is associated with chronic steatorrhea As a result of the faulty digestion and absorption of fat insoluble calcium salts are formed and the fat soluble vitamin D is excreted in the excess fat This has been well demonstrated by various investigations carried out in cases of osteomalacia

In the mild form of osteomalacia the patient may complain only of weakness or of pains in the bones of the legs or in the lower part of the back while standing or walking In cases of severe osteomalacia the patient may seek medical aid because of the distressing symptoms of severe tetany Another patient may suffer from a crushed vertebra resulting from moderate lifting or a minor fall In cases of advanced disease severe backache is the most common symptom This pain is aching in character often is generalized and is worse in the winter, when there is greater deficiency of vitamin D than at other times Muscular weakness may be marked and a waddling gait is not uncommon Often there is marked sensitivity of the bones to light pressure The skeletal deformities are numerous In the roentgenogram generalized osteoporosis thinning of the cortices bowing fractures and deformities of various types are evident

The diagnosis of osteomalacia is not particularly difficult, if the physician suspects its presence Tetany occurring in association with chronic diarrhea or a calcium-phosphorus deficiency always should suggest osteomalacia Any skeletal disease characterized by generalized decalcification such as the osteoporotic forms of hyperparathyroidism senile osteoporosis and the like may be mistaken for osteomalacia The treatment of osteomalacia is essentially the same as the treatment of rickets

that this be remedied rapidly by the administration of calcium salts The usual method is to administer 3 or 4 gm of calcium chloride intra venously as an initial dose This should be followed by a dose of 1 gm 4 times daily for 2 or 3 days and then by 1 gm twice a day for 5 to 7 days In the administration of vitamin D a program similar to that de scribed for the treatment of rickets may be followed

Having made a diagnosis of rickets determined which method of treatment to use and used it the physician now is confronted with the problem of how to ascertain if this therapy is accomplishing the desired results The best way to do this is to determine the concentration of cal cium and phosphorus in the serum If the concentration of calcium is within normal limits and the concentration of inorganic phosphate rises to 5 mgm per 100 c c vitamin D therapy is succeeding In ordinary cases in which the usual doses are administered the concentration of the serum phosphates may be expected to reach normal on about the tenth day of treatment In the absence of chemical and roentgenological exam inations appraisal of treatment becomes very difficult bony deformities disappear very slowly Perhaps the best clinical indication that therapy with vitamin D is succeeding is improvement in muscle function as evi denced by efforts on the part of the child to walk or to sit up He seems to gain strength and becomes more active The bony deformities gradu ally disappear and the bones acquire an increased degree of rigidity

Methods of preventing the occurrence of rickets should be common knowledge to every physician For preventive measures the importance of commencing administration of the vitamin early and reaching the full dose by the end of the second month of the infant s life cannot be re peated too often[3] It is best to begin with a dose of a half teaspoonful c c of cod liver oil 175 units after a few days this may be increased to 1 teaspoonful 4 c c or 350 units and in the next 2 weeks raised to 2 teaspoonfuls 8 c c or 700 units Use of this dose should be continued until the child is 2 years of age If there is any reason to suspect that the child may be susceptible to rickets the dose should be increased during the first year so as to supply 1 000 units of vitamin D daily

Irradiated milk does not exhibit sufficient potency in vitamin D for the prevention of rickets in cases in which a susceptibility exists Sunlight may be relied on for the prevention of rickets in the summer months but in the winter for all practical purposes the rays of the sun may be re garded as devoid of antirachitic rays

roentgenological examinations, the dose of vitamin D can be reduced to a preventive level In cases in which older children are hypersusceptible to rickets, it may be necessary to continue the administration of large doses, the increased requirements of the premature infant usually are transitory

The treatment of active rickets with large single doses of vitamin D administered parenterally has received considerable attention during the past few years[1-4] Administration of 500,000 to 1,000 000 U S P units of vitamin D to children who had rickets including premature infants, has been followed by rapid healing without clinical evidence of toxicity (Fig 12) In these cases the value for serum phosphatase may become normal as early as the fifth or sixth day, and roentgenographical evidence of healing also may be noted

Many have believed that infants can be protected successfully from rickets for the whole of one winter by the ingestion of a single large dose of vitamin D Recently Krestin[35] made a clinical trial of the procedure using full-term infants and children from 2 months to 3 years of age who showed no radiological or clinical evidence of rickets On the basis of results of his study, he suggested that, when a child is first seen in late winter or spring one dose of 7 5 mgm of calciferol vitamin D having an activity of 300,000 international units probably is sufficient for protection until the next winter When the child is seen for the first time in fall or early winter, the dose should be repeated after three months For premature infants and those recovering from marasmus or acute illnesses larger and more frequently administered doses may be necessary

There are occasional cases in which rickets does not respond to treatment with the usual amounts of vitamin D[6,7] In some cases rickets is due to a disturbance of the acid base balance and has been treated successfully by the administration of sodium bicarbonate or by the use of massive doses of vitamin D The quantity of vitamin D needed may be so large that it approaches dosages that are definitely toxic While the maintenance dose is being established it is desirable to examine the urine every 1 to 3 days for albumin erythrocytes and calcium casts The blood calcium should be determined weekly and should not be allowed to rise above 12 mgm per 100 c c if the dosage exceeds 20 000 units daily for an infant or 50 000 units for a child Administration of the vitamin should be discontinued if anorexia or nausea appears

In the treatment of rachitic tetany it is important that the effects be produced rapidly It has been pointed out that the primary derangement in tetany is in the concentration of serum calcium, and it is necessary

added advantage of increased stability over that of tocopherol It has been suggested that synthetic racemic tocopherol tocopheryl acetate be made the international standard for vitamin E, and the suggestion has been adopted The international unit is the vitamin E activity of 1 0 mgm of the standard preparation racemic tocopherol acetate in olive oil The quantity represents the average amount which prevents resorption gestation in rats deprived of vitamin E when the substance is administered orally[64, 65]

Physiology and Pathology

These fat soluble vitamins E and their esters are in the presence of bile acids easily absorbed from the intestinal tract[66] and on intake of esters *the free vitamin appears in the blood Excess doses cause the excretion of* a certain amount in the feces but only traces are found in the urine This suggests that the vitamin is inactivated in the organism probably by an oxidation mechanism These vitamins are stored in very small amounts in animal body fats in the muscles and in the anterior lobe of the pituitary *gland*

In animals a lack of vitamin E manifests itself chiefly by changes in the reproductive mechanism it was on the basis of this observation that the terms antisterility vitamin and reproductive vitamin were derived In the presence of vitamin E deficiency conception occurs in the *female rat but it is followed by resorptive sterility In the male rat* degeneration of the germinal epithelium and spermatozoa develops to the point of complete loss of reproductive power

For a number of years interest was centered exclusively on the role which this vitamin played in reproduction It seems that such an action *was too narrow a definition of its function In the absence of vitamin E* in the diet of many animals muscular dystrophy and a characteristic paralysis of the hindquarters have been shown to develop[7, 68, 69] Although vitamin E appears essential for the integrity of the skeletal muscle of many species the relationship of these disturbances to human muscular dystrophies is by no means clear *It has been suggested that it is concerned* in some way with the contractile phase and increased oxygen uptake in the muscle tissue has been observed during vitamin E deficiency[70] This possible relationship to human muscular disturbances remains an inviting subject for further investigation

Recently another activity of vitamin E has been recognized In a series of studies Hickman and associates[1 73] have shown that natural

VITAMIN E

Chemistry

As early as 1922 a new factor, most abundantly present in wheat germ oil, was demonstrated as needed in the rat for the successful completion of pregnancy in the female and for continued fertility in the male In 1936 this factor was identified successfully as alpha tocopherol (Evans, Emerson and Emerson)[5] Fernholz[60] in 1938 proposed the formula for alpha tocopherol on the basis of oxidative degradation with chromic acid, and synthesis was accomplished later independently in three laboratories[61] (Fig 13)

Three factors have been isolated from natural material namely alpha, beta and gamma tocopherol Beta tocopherol and gamma tocopherol are homologues of the natural substance and have almost identical properties but slightly less biological activity Natural gamma tocopherol

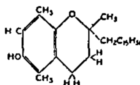


Fig 13 Structural formula for alpha tocopherol

is approximately 50 per cent more potent than synthetic dl gamma tocopherol, and natural beta tocopherol is about 100 per cent more active than synthetic dl-beta-tocopherol[6] These substances are readily soluble in lipid solvents but are only slightly soluble in water Although stable at high temperatures (200° C), they rapidly lose their activity in the presence of ultraviolet light or mild oxidizing agents The long recognized resistance to rancidity of vegetable oil that contains vitamin E might be cited as an everyday example of its oxidation inhibiting quality

There are numerous compounds related to the tocopherols which have been shown to exhibit vitamin E activity, but they do so in a limited manner when compared to tocopherol Of some special interest is naphtho-tocopherol, which shows vitamin E activity in 25 mgm doses but also shows vitamin K activity in doses of from 300 to 600 gamma[6] The tocopherols themselves have a certain structural specificity and the removal of a methyl group from the aromatic nucleus or the aliphatic side chain greatly diminishes the vitamin E activity of the substances The acetate of tocopherol is equal in biological activity and possesses the

E the results have been most discouraging Recently however Milhorat and Bartels[17] have suggested that tocopherol forms a condensation product with inositol in the gastrointestinal tract and that the inherited defect in muscular dystrophy is a deficiency in this reaction of condensation These and other more recent suggestions stimulate hope that vitamin E is a factor to be reckoned with in human physiology and perhaps in human disease[18]

vitamin E enhances the growth promoting power of vitamin A alcohol and vitamin A acetate The vitamin A activity of carotene is markedly influenced also by the intake of tocopherol It is suggested that this sparing action on the A vitamins is due chiefly to repression of oxidation in or near the gastrointestinal tract Recently it has been shown also that tocopherol increases both the storage of vitamin A in the liver and the stability of carotene in the intestinal tract It appears that the role of tocopherol as an intestinal antioxidant has been established[11]

We have no exact knowledge of the quantitative requirements of man for vitamin E We lack also precise assays of the vitamin E content of foodstuffs Apparently vitamin E occurs in most foods, and it is noteworthy that one of the greatest obstacles which investigators encountered was in obtaining a diet deficient in this vitamin Wheat germ oil is the richest source of vitamin E, but also it is found in considerable amounts in cottonseed oil, lettuce oil, rice-germ oil and other seed germ oils

Various authors have used wheat-germ oil in doses varying from 0 5 c c to 6 c c daily and it may be of significance that any apparent success was the same in spite of any variation in the dose used Toxic reactions have not been reported in cases in which small doses were administered and large doses of wheat-germ oil have given rise to only minor symptoms The danger of production of neoplasms by the use of such oil appears to be nonexistent

A chemical method for the determination of tocopherols in blood plasma has been described and in a small series of cases values for tocopherol in human normal plasma were found to average 1 .0 mgm per 100 c c

Clinical Use of Vitamin E

Whether or not avitaminoses occur in man has not yet been definitely decided Vitamin E has been used in the treatment of many clinical ills but to date justifiable conclusions have been difficult to make

There is some evidence to support the view that vitamin E may exert a beneficial influence in certain cases of habitual abortion [6], threatened abortion and abruptio placentae In the presence of male and female sterility menstrual disturbances the toxemias of pregnancy faulty lactation and vaginal pruritus the reported results are at variance and cannot be accepted until further evidence has accumulated

In the treatment of human myoneurogenic disturbances with vitamin

1,4-naphthoquinone with the exception that vitamin K_1 has a phytyl side chain in the three position. The synthetic product also is identical with natural vitamin K_1 which is obtained from alfalfa. Exposure to sunlight destroys the vitamin activity of alfalfa within several hours although if artificial light is used little destruction is observed within 24 hours. The pure preparations, however, are destroyed by both sunlight and artificial light. Under ultraviolet light rays the oxide of vitamin K_1 is about 3 times as stable as vitamin K_1 but has the same clinical effect as vitamin K_1.[4] A large part of the activity of concentrates of vitamin K is destroyed by alkali, by strong acids and by aluminum chloride. The vitamin is fat soluble and at low temperatures forms yellow crystals.

Vitamin K_2 is another natural vitamin K and was isolated first from putrefied fish meal. The structure of this vitamin still is under discussion. Some investigators believe the probable structural formula is 2-methyl-3-difarnesyl-1,4-naphthoquinone with an empiric formula $C_{41}H_{56}O_2$. This compound is also fat soluble and has been obtained as light yellow crystalline flakes.

The demonstration of the quinoid structure of the vitamins K has stimulated great study of the many substances which possess a quinoid nucleus. The first report of a synthetic compound having antihemorrhagic activity was made by Almquist and Klose who found that phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) possesses marked antihemorrhagic activity but that it is only 1/500 as active as vitamin K_1. Phthiocol is the yellow pigment found in the human tubercle bacillus. Of all the naphthoquinone derivatives studied 2-methyl-1,4-naphthoquinone has proved to be the most active. This compound can be synthesized by the oxidation of 2-methyl naphthalene. This material is very slightly soluble in water. In solution its activity is impaired by sterilization with steam; therefore it is rather unstable unless special precautions are taken. This compound is so active that several investigators have suggested that it be adopted as a basic standard for assay of vitamin K. By some assays this compound has been found to be about three times as potent, on a basis of weight, as vitamin K_1. Because of the great usefulness of this compound in clinical medicine the Council on Pharmacy and Chemistry of the American Medical Association on the recommendation of the Committee on Nomenclature authorized the use of "menadione" as a nonproprietary name for this substance.[5]

Many other compounds have been tested for vitamin K activity. Most of those which have such activity are basically 1,4-naphthoquinone or the corresponding hydroquinone; a few, however, are not. The com-

VITAMINS K

The introduction of vitamin K in clinical medicine came as a result of an observation of Dam and his associates[9,81] of Copenhagen, Denmark. They showed that a deficiency disease could be produced in chicks subsisting on feed washed in ether and could be cured by the administration of an antihemorrhagic material present in hog liver fat, hemp seed and certain cereals and vegetables. Later it was shown by these investigators that deficiency in this dietary factor resulted in diminution in the amount of prothrombin in the circulating blood which led to fatal hemorrhagic diathesis. The term "vitamin K" was proposed by Dam as an abbreviation of the name "Koagulations Vitamin" to apply to the substance that was necessary for the prevention of a nutritional deficiency disease in chicks. Soon it was suggested by Quick of the United States that deficiency of vitamin K might be present in patients who had obstructive jaundice. These suggestions now have been confirmed amply and extended and within a relatively short time various workers in this country and abroad[9-8] have demonstrated that vitamin K under most circumstances is a specific remedy for deficiency of prothrombin.

CHEMISTRY

In 1939 McKee and his associates reported the isolation of vitamin K_1 from alfalfa and of vitamin K_2 from putrefied fish meal and presented

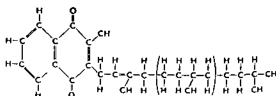


Fig. 14. The structural formula of vitamin K_1 (-methyl-3-phytyl-1,4-naphthoquinone).

evidence to indicate a quinoid structure of these vitamins. For the final isolation and synthesis of vitamin K_1 Doisey and his associates, Almquist and Klose, Fieser and his associates, Dam, Karrer and co-workers are responsible. Independently these groups of investigators reported the structure of the vitamin K_1 molecule to be -methyl-3-phytyl-1,4-naphthoquinone (Fig. 14). This vitamin is identical with -methyl-1,

It has been shown that 2 methyl-1 4 naphthoquinone is bacteriostatic and bactericidal for both gram positive cocci and gram negative bacilli, and similar effects have been noted in the case of many fungi. The mode of action apparently consists of the blocking of essential enzymes through combination with sulfhydryl groups. This mode of action is similar to that suggested by other investigators for several antibiotic agents including penicillin[89]

Little is known concerning the action of vitamin K in the animal organism. It has been well demonstrated that this vitamin and related compounds have some relationship to the blood clotting mechanism. Avitaminosis K produces a decrease in the prothrombin level of the blood which increases rapidly after the administration of vitamin K. Vitamin K does not form a part of the prothrombin molecule since orally administered prothrombin does not show vitamin K activity. The manner in which vitamin K participates in the formation of prothrombin is not known. It has been suggested that vitamin K is a reversible oxidation reduction catalyst the hydroquinone form of which is oxidized readily by molecular oxygen. This reversible character of the vitamin may be used to explain the fact that small quantities produce the characteristic effect[90]

More recently a hypothesis has been reported which suggests that the antihemorrhagic effect of vitamin K and its synthetic analogues is due to biochemical degradation to phthalic acid and that it is largely a function of their capacity to be transformed into the latter[91] The authors[92] who advanced such a hypothesis regard phthalic acid as the true carrier of biological activity and suggest that natural vitamin K and its synthetic analogues be regarded as provitamins. Recently these authors have isolated phthalic acid from the urine of man and of the dog after the administration of menadione. Menadione itself was not found in the urine whereas administered phthalic acid was excreted quantitatively and unchanged. These finding have some strong suggestive supporting evidence. Dicumarol a vitamin K antagonist owes its activity to degradation to a simpler compound namely salicylic acid. The vitamin K compounds may owe their antihemorrhagic activity to their easy degradation to phthalic acid. The attractive hypothesis which results is that the antagonism of dicumarol to vitamin K is due to the competition in vivo of two structurally similar molecules. Phthalic acid possesses two carboxyl groups on a benzene ring salicylic acid possesses one carboxyl and one hydroxyl group. The competition of structurally

pounds 4-amino-2-methyl-1-naphthol hydrochloride and 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate, are water soluble and therefore, have proved to be of considerable use clinically. These compounds are not so active as 2-methyl-1, 4-naphthoquinone, but they are active enough to produce desired clinical results. Apparently these derivatives of the simpler quinones are utilized more efficiently than are the corresponding derivatives of the natural vitamins. A monosodium bisulfite of menadione has been given the nonproprietary name of "menadione bisulfite"; it is also an active water-soluble derivative of menadione.[88]

Physiology

Many investigators have shown that the presence of bile in the intestinal tract is essential for proper absorption of the fat soluble vitamin K and there is, futhermore, some evidence to suggest that these fat soluble compounds are absorbed better, if other fats are present in the intestinal tract. Clinically it is well established that the presence of bile or more correctly the presence of adequate amounts of bile salts is required for the proper absorption of vitamins K. The exact point of absorption in the intestinal tract is not known, but clinical experience indicates that concentrates of vitamin K are not absorbed through the colon or upper part of the ileum, but that they are absorbed readily through the upper part of the small intestine. Recently it has been reported that excessive amounts of liquid petrolatum administered with meals may prevent proper absorption of this vitamin.

The vitamin is not stored readily in the body but it has been found in the livers of lower animals in relatively small amounts. Greaves has shown that in the liver of the rat vitamin K is not stored in appreciable amounts. Results of clinical work would indicate that the same observations are applicable to the human being. In so far as is known vitamin K is not present in the urine. It can be demonstrated in the feces but whether it is there because the feces merely hold the organisms which are known to contain vitamin K, or whether the presence of the vitamin in feces is referable to real excretion of vitamin K, remains to be established. The vitamin is not present in human bile collected under sterile conditions. In chicks subsisting on a normal diet the spleen, red muscle, gizzard, bone marrow and pancreas were found to contain relatively large amounts of vitamin K, whereas the liver and lungs were found to contain somewhat less.

considerably prolonged In animals the principal symptom to appear during deficiency of vitamin K is the occurrence of hemorrhage

In chicks fed on material deficient in vitamin K there develop subcutaneous intramuscular and internal hemorrhages profuse bleeding *from minor abrasions and a delayed clotting time associated with a low* content of prothrombin in the plasma Injuries in a wide sense may determine the occurrence and severity of these hemorrhages Results of studies by many investigators of the content of prothrombin in the plasma in hemorrhagic chick disease show that hemorrhages do not occur until the content of prothrombin has declined to about 10 to 15 per cent *of normal It has been indicated that the clotting time is delayed only* if the content of prothrombin has declined to less than 30 or 40 per cent of normal Thus early in the course of the disease when deficiency of the vitamin is less severe the content of prothrombin in the plasma may be reduced considerably and yet the clotting time will remain normal This is extremely important as a clinical factor Deficiency *of prothrombin also has been produced in rats mice ducklings* young geese pigeons canaries and rabbits that were subsisting on diets deficient in vitamin K

It has been long known that in dogs which have biliary fistulas an abnormal tendency to bleed develops in addition to many pathological complications Furthermore it has been pointed out that continuous *subsequent feeding of bile to such animals will correct this abnormality* *This tendency toward bleeding of dogs which have biliary fistulas was* shown later to be caused by deficiency of prothrombin which could be corrected by the administration of vitamin K In rats which have renal biliary fistulas there is likewise a diminution in the circulating prothrombin which can be corrected by the administration of vitamin K

Deficiency of vitamin K can be produced also by alteration of the bacterial flora of the intestinal tract *It was observed first that hypoprothrombinemia developed in young rats given* sulfaguanidine in purified diets and that the effect on the content of prothrombin in the blood could be counteracted by the administration of vitamin K[93] It was found that the hypoprothrombinemic effect of this drug could be prevented by the administration either of p-aminobenzoic acid or of a liver friction[94] Sulfapyrazine sulfadiazine or sulfathiazole when fed to rats at a *1 per cent level in purified diets results in the regular production of* severe hypothrombinemia within to 3 weeks Sulfaguanidine sulfanilamide and succinyl sulfathiazole are much less effective in producing

similar molecules, acting as either substrates or co enzymes for enzyme systems, is common knowledge among chemists

In so far as is known at present, vitamin K has no relationship to immunity, infection, pregnancy and lactation, the nervous system gastro-intestinal tract or cardiovascular system but it is associated intimately with normal physiological function of the liver and with proper coagulation of the blood Its exact role in coagulation of the blood is not known It is known to be necessary for proper formation of prothrombin, but the manner in which this is accomplished remains to be determined A deficiency of vitamin K arising from any cause produces a deficiency of prothrombin in the circulating blood, and in all instances except those in which there is severe hepatic damage, this deficiency of prothrombin can be corrected by the proper administration of vitamin K

SOURCES

Among the richest sources of vitamin K_1 are the green leafy tissues of spinach alfalfa kale, cauliflower carrot tops and chestnuts Tomatoes hemp seed and soy bean oil also are good sources but fruits and cereals are poor sources of the vitamin The parts of the plant which contain chlorophyll, usually have the largest amounts of vitamin K

Vitamin K occurs in many bacteria, whereas yeast, molds and fungi contain little or no vitamin K The vitamin K activity of feces of the horse, cow, sheep, hog and man has been well established Apparently during the growth of the bacteria the vitamin K is synthesized and is retained within the bacteria, since the filtrate of the culture medium, which is free of the bacteria, contains none of the vitamin Ether extracts[83] of these bacteria, however, have vitamin K activity Dried human feces both normal and acholic are rich in the vitamin, but the vitamin K activity of feces undoubtedly results from the bacterial content within them

Most animal materials contain very little vitamin K Milk and eggs contain small amounts, and hog liver is very rich in this vitamin

EXPERIMENTAL PATHOLOGICAL PHYSIOLOGY

In the presence of deficiency of vitamin K the prothrombin content of the blood is markedly decreased and the blood clotting time may be

First after ingestion of a diet inadequate in vitamin K This condition is rare but the clinical observation is well supported by the experimental production of low values for prothrombin in the blood of rabbits and mice after they have been caused to subsist on diets deficient in vitamin K

Second in the presence of inadequate intestinal absorption This may result from (1) lack of bile in the intestine because of decreased secretion of bile salts (2) obstruction of the bile duct from any cause or (3) inadequate absorption attributable to various intestinal lesions

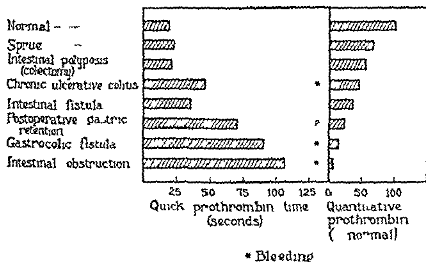


Fig 15 The various intestinal disturbances with which may be associated a deficiency of prothrombin that can be readily corrected by the proper administration of compounds with vitamin K activity (Butt H R and Snell A M Vitamin K W B Saunders Company Philadelphia 1941)

such as intestinal obstruction and short circuiting surgical procedures It likewise has been demonstrated that severe diarrheal diseases such as ulcerative colitis sprue or celiac disease may result in deficiency of prothrombin[101] (Fig 15) A deficiency of prothrombin as a cause of bleeding in cases of various intestinal disturbances is something new in clinical medicine Although instances of deficiency in prothrombin referable to the effect of intestinal disturbances are not often encountered they do comprise a rather distinct group and one which warrants close observation When patients who have extensive disease of the intestine such as sprue chronic ulcerative colitis intestinal obstruction or ileitis or who

this phenomenon[9] The action of these drugs is thought to be the result of their effect on coliform organisms in the intestinal tract[96]

It has been reported that female rabbits fed a vitamin K deficient diet for 40 days and mated with normal males aborted during the late first or early second trimester of pregnancy Retroplacental hemorrhages were considered responsible for the abortions, and although the content of prothrombin was lowered in the rabbits it did not reach a critical level If the females were bred once more while they were subsisting on the deficient diet, abortions occurred but normal term pregnancies resulted when vitamin K was added to the diet[9]

Human Requirements of Vitamin K

Although it has been shown experimentally that vitamin K is required by the chick goose, duck, canary, pigeon turkey rat rabbit mouse, dog and man[99], yet the exact amount of vitamin K required by these various species is unknown It is known however that pure vitamin K_1 or synthetic compounds which exhibit vitamin K activity in doses of 1 to 2 mgm, are capable of correcting deficiency of vitamin K in most instances In diseases, in which there is acute or chronic hepatic damage of a severe degree, even large doses of vitamin K are ineffective in correcting the deficiency of prothrombin In deficiency of prothrombin, produced in the human being by the administration of dicumarol [3,3′-methylenebis (4-hydroxycoumarin)], as much as 40 mgm of menadione may be needed to correct the hypoprothrombinemia

As a rule, large doses of vitamin K when administered to man do not produce hyperprothrombinemia but the oral administration of large doses of menadione to the dog rabbit or rat induces this condition which may persist for several days[93]

The discussion of requirements of vitamin K for the human infant is reported under the section entitled Deficiency of prothrombin among newborn infants"

Deficiency of Vitamin K in Man

There are a number of conditions in which a deficiency of prothrombin exists or can be produced in man that can be corrected by the administration of vitamin K[100] Such a deficiency may occur in any of the following circumstances

dence suggests that the synthesis of prothrombin is prevented. This occurs either through the same mechanism, which prevents vitamin K from catalyzing prothrombin synthesis, or through a direct action on the prothrombin[105]

At the low levels of menadione which ordinarily would correct a nutritional deficiency of vitamin K the hypoprothrombinemic action of dicumarol is not prevented. Large doses of vitamin K, however, will correct the deficiency of prothrombin produced by dicumarol[10, 110, 111]

DEFICIENCY OF PROTHROMBIN AMONG NEWBORN INFANTS

It is rather generally agreed that during the first few days of an infant's life a deficiency of prothrombin exists in the circulating blood. Waddell and Guerry and their associates[11] were the first to report the important discovery that this physiological deficiency of prothrombin of newborn infants and the bleeding tendency which sometimes developed could be corrected by the administration of vitamin K. Since that time numerous reports have appeared concerning the effect of the various compounds possessing vitamin K activity on the content of prothrombin of newborn infants and the effect of such compounds on the hemorrhage which occurs frequently. The important suggestion also has been made that the deficiency of prothrombin existing at the time of birth might account in many instances for the intracranial hemorrhages which sometimes follow protracted labor and which result frequently in permanent paralysis of the infant.

In Fig. 16 are plotted the prothrombin levels during the first 6 days of life as reported from various laboratories which employed a variety of methods for the measurement of prothrombin in the blood. On the basis of this figure one would be justified in concluding that the clinical material studied in these various cities was different and that each undoubtedly represents specialized classes of patients studied under special conditions. Smith and Warner[113] believed that the clue to these discrepancies lies in the fact that the vitamin K intake of the pregnant woman has much to do with the amount of the vitamin received by the infant and hence with the content of prothrombin of the latter. Waddell and Guerry[114] have shown that the content of prothrombin in the newborn infant is much higher in summer than in winter. This probably results from the large intake of green vegetables during the summer months. The results recorded in the summer are shown in curve 4A (Fig. 16) and the results obtained in winter appear in curve 4B.

have undergone multiple short circuiting operations on the intestinal tract experience hemorrhage either before or after surgical treatment, deficiency in prothrombin should be recognized and corrected before other forms of treatment are instituted One of the most important points in the management of these conditions is that the physician follow the content of prothrombin in the blood closely before and after operation in all cases of abnormalities of intestinal mucosa, particularly in cases in which the postoperative condition requires continued aspiration of gas and secretions from the intestinal tract This practice has solved the mystery of obscure intestinal bleeding, which occurs frequently in such cases, and definitely has reduced postoperative morbidity and fatality

Third injury to the liver There is, of course, considerable evidence both clinical and experimental, to indicate that the liver plays an active part in the formation of prothrombin, and that any severe injury to this organ results in a deficiency of prothrombin[10] It has been well demonstrated clinically and experimentally that primary hepatic disease such as cirrhosis, liver atrophy or chronic hepatitis frequently is accompanied by deficiency of prothrombin This deficiency of prothrombin is not the result of deficiency of vitamin K but apparently is the direct result of severe hepatic damage Under these conditions the deficiency of prothrombin usually is not relieved by the administration of vitamin K in any amount It is well to recall that instances of severe hepatic damage occur in any disease in which the liver might be involved and although this group of cases is somewhat small this possibility must be kept in mind

Fourth, ingestion of salicylates It has been reported that when salicylates are administered to man there is a reduction of prothrombin in the circulating blood[103,104,10], and that this deficiency of prothrombin can be corrected by the administration of vitamin K[106] These facts now have been confirmed amply The effect of salicylates however, even in large doses on the prothrombin content of the blood is not great, and the occurrence of hemorrhagic manifestations is unlikely[107] If any surgical procedure is contemplated for, or arises as an emergency in a patient who is ingesting large amounts of salicylates, then vitamin K obviously should be given before and after operation

Fifth, ingestion of dicumarol When this compound is administered to animals or to man there results after action in vivo a decrease in the prothrombin content of the circulating blood The mechanism through which the content of prothrombin is reduced, still is obscure, but evi

the newborn infant is unable to secrete sufficient bile that the absorption of fat is very limited and that gastrointestinal hypermotility is the rule *Thus even though vitamin K is present proper absorption of the* vitamin would be theoretically unlikely until the digestive function approaches normal This occurs on about the third or fourth day of life To support the suggestion that the presence of bacterial flora in the intestinal tract is connected intimately with the return of the value for *prothrombin to normal at the end of the third day some investigators* have shown that extra feeding started within _ hours after delivery of the infant can prevent the subsequent development of hypoprothrombinemia Evidence which tends to refute these theories will be discussed a little further along

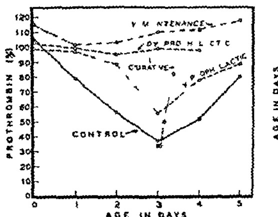


Fig 17 The response of infants to variable doses of vitamin K The compound used as a source of vitamin K activity was the water soluble 4 amino 2 methyl 1 naphthol (synkamin) Administration was by intramuscular injection (Smith H P and Warner E D Vitamin K Clinical Aspects in The biological action of the vitamins a symposium Edited by E A Evans Jr The University of Chicago Press *Chicago 1942*)

It has been shown by Sells Walker and Owen[115] that the minimal vitamin K requirement of the infant is extremely low Their results *modified by Smith and Warner*[113] *are shown in Fig 17* The uppermost curve in this figure shows that 1 microgram of vitamin K given daily is adequate to maintain the content of prothrombin at normal It is also shown in the second curve that a dose of 10 micrograms usually would prevent the decrease shown in the untreated controls In Fig 17 also is seen a curve which shows that if 1 microgram is given on the third day

The exact cause of this deficiency of vitamin is not completely known. It has been suggested that as soon as the presence of bacterial flora of the intestinal tract is established, the infant is capable of synthe-

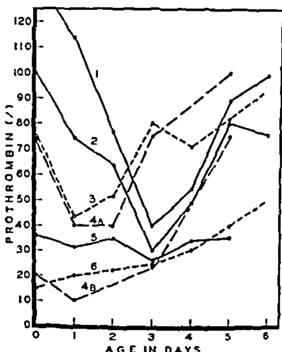


Fig 16 The content of prothrombin in the blood of an untreated infant during the first six days of life. Curves 1 and 2 were devised by Owen, Hoffman, Ziffren and Smith in Iowa City. Curve 1 is based on the bedside test. Curve was devised according to the method of Quick. Curve 4A and 4B were prepared by Waddell and Guerry (114) in Charlottesville, Virginia; they used a microadaptation of Quick's method by Kelly and Gray. Curve 4A was charted during winter and early spring; curve 4B was computed during late spring and early summer. Waddell and Guerry expressed their results in the form of the prothrombin time (in seconds). To facilitate comparison these values have been converted into percentage of normal adult values with the aid of the conversion curve of Quick. Curve 5 was prepared by Owen, Hoffman, Ziffren and Smith in Iowa City. They employed the two stage prothrombin method of Warner, Brinkhous and Smith. Curve 6 was computed by Kato and Poncher in Chicago; they utilized a micromethod devised by Kato. (Smith, H. P. and Warner, E. D.: Vitamin K. Clinical Aspects, in The Biological action of the vitamins, a symposium. Edited by E. A. Evans, Jr. The University of Chicago Press, Chicago, 1942.)

sizing vitamin K, a fact which has been well proved experimentally. This explanation, however, does not explain the delay in the return to normal of the value for prothrombin, a delay which occurs in many infants. To explain this phenomenon it must be recalled that the liver of

of menadione given by mouth to a mother a half hour to forty eight hours before delivery is effective in preventing hemorrhagic disease of the newborn infant[114]. There is good evidence to indicate that, although the feeding of vitamin K to the infant after birth increases the concentration of prothrombin, the concentrations in these instances are not so high as those achieved by antepartum administration of the vitamin to the mother.

Many workers believe that instances of cerebral hemorrhage occurring in the course of birth with minimal trauma are precipitated by small hemorrhages which endure for a number of days. For this reason many workers interested in this problem believe that the lives of some of the infants concerned might be saved if the blood at birth exhibits better properties of coagulation. Most investigators believe that some form of vitamin K should be administered to every mother at the onset of labor. Some still insist that the vitamin also should be given to the newborn infant as an added precaution. In any event, the plan is so simple, the vitamin so cheap and the toxic reactions so minimal that this program should be adopted universally in the hope of preventing injury at birth[179].

Methods for Measuring Deficiency of Vitamin K

Since no international standard of units has been established for vitamin K, many methods of assay and standards of units have arisen[1,2]. The wide interest displayed in vitamin K and associated naphthoquinones has given rise to the need for convenient and accurate methods for their estimation. A step in this direction was made by Trenner and Bacher[125], who described a method by which many quinone-like substances can be assayed. Others recently have also reported work in this direction[123,1,4,2].

Of clinical importance are the methods by which deficiency of vitamin K can be recognized by simple laboratory procedures. Several excellent methods for the measurement of deficiency of prothrombin in the blood of man have been described, but in the experience of many the method developed by Quick and his associates[126,1, 1-4,129,130,131,133] has been found adaptable for general use in the clinical laboratory. The method developed by Warner and his associates[123,1,4,1] also is used, with modification, in many laboratories. *Details of these methods are given in several publications*[3,4,1,7,2,8,129,130,131,33].

The so-called bedside method has come into considerable use and is reported to be of great value for the general practitioner. Suitably compact sets for making this measurement at the bedside now are available

of life it is followed in 10 hours by an increase in the content of prothrombin from 30 per cent of normal to the percentage of 95

As already mentioned, nearly all investigators have noted that the content of prothrombin increases until it has exceeded the so called danger point as soon as the infant receives an adequate amount of milk It always has been assumed that milk, since it was a poor source of vitamin K served merely to introduce bacterial flora into the intestinal tract and that vitamin K was produced by these bacteria The work of Sells Waller and Owen[11] has shown, however that milk does contain an amount of preformed vitamin K adequate to meet the minimal requirements of the infant

To recapitulate, it appears that, when large amounts of vitamin K are given to the pregnant female the vitamin is transmitted through the placenta and that some is stored in the fetus According to Smith and Warner[113], if the diet of the mother has been adequate, the content of prothrombin in the infant is at a safe figure at birth Frequently this is not the case, and because of the infant's lack of food intake a deficiency of vitamin K develops rather rapidly During the critical 4 days that follow birth, a single prophylactic dose of 10 micrograms is sufficient to maintain a normal content of prothrombin If the mother is given 1 mgm of the vitamin similar protection results It seems that the vitamins may be distributed between mother and fetus almost in proportion to body weight Apparently the infant is competent to manufacture adequate amounts of prothrombin, if vitamin K is present in sufficient amounts

On the basis of work, reports of which are now available, it appears that a dose of from 0 5 to 1 mgm of 2-methyl-1 4 naphthoquinone or of any of the other synthetic quinone compounds available commercially is sufficient in most instances to control certain hemorrhagic disease of the newborn and that, if it is administered at the time of birth it will prevent transitory hypoprothrombinemia It must be remembered that failures also can occur in the treatment of infants, if sufficient hepatic damage has occurred

It has been reported and well established by several groups of workers that the administration of vitamin K to mothers prior to delivery will prevent the usual decrease in the content of prothrombin in the blood which is observed among newborn infants and that the administration of vitamin K to the newborn infant also will increase the concentration of prothrombin in the plasma[116 117 118]

On the basis of results of work now available it appears that mgm

struction Hemorrhage usually is noted between the first and fourth postoperative days but it may appear as late as the twelfth to eighteenth day after operation As is well known cholemic bleeding ordinarily begins as a slow oozing from the operative incision from the gums or nose or from the gastrointestinal tract Often however the first evidence of hemorrhage is afforded by the appearance of severe hematemesis or *melena Such bleeding often is controlled temporarily by the transfusion* of whole blood but all too frequently even the repeated transfusions of blood fails to control the hemorrhagic diathesis Bleeding of this type in our experience and in the experience of many others invariably is associated with prolongation of the prothrombin clotting time

Bleeding of patients suffering from jaundice occurs most often in the presence of those conditions in which bile is excluded completely from the gastrointestinal tract such as complete biliary obstruction produced by neoplasms of the pancreas ampulla and gallbladder Postoperative stricture of the common bile duct is accompanied perhaps by the second highest incidence of bleeding intermittent obstruction caused by the presence of stones comes third Complete external fistulas are relatively rare but often are associated with bleeding Although bleeding is more likely to occur in those cases in which bile is excluded completely from the intestine yet the physician must not overlook the fact that bleeding also can occur in the absence of jaundice if the liver has been injured considerably as the result of chronic cholecystic disease Although the foregoing facts are somewhat useful for prediction of whether or not a patient will bleed the exceptions are so frequent that rigid clinical rules cannot be devised

It has been well demonstrated experimentally that if the hepatic parenchyma is injured the amount of prothrombin in the circulating blood decreases *It has been demonstrated further by Warner and his* associates and by Bollman and his associates that if the hepatic damage in these animals is too severe the content of prothrombin in the circulating blood does not increase after the administration of vitamin K Likewise it has been well demonstrated clinically that patients who have severe hepatic damage have a decrease in the prothrombin in the circulating blood and that occassionally they will not respond to the administration of vitamin K

These instances of severe hepatic damage can occur in any disease in which the liver might be involved but most frequently they are seen in cases of cirrhosis of the liver in those in which obstruction or stricture of the common duct has existed over long periods and in those in which

commercially[1 3] Several micromethods for the measurement of deficiency of prothrombin of infants also have been described and are used routinely in many institutions[134 13 136 13 1 8]

It must be admitted that all current methods for the estimation of prothrombin are, of necessity, indirect However, certain of these methods for the measurement of prothrombin are the most nearly accurate methods available at present for estimation of the tendency of a patient to bleed in the presence of suspected deficiency of prothrombin The information afforded by the measurement of prothrombin in the circulating blood is much more nearly accurate in the prediction of the tendency of a patient to bleed than is the measurement of the coagulation or bleeding time as formerly used in the consideration of such tendencies

Toxicity

To date no serious untoward reaction has been observed among persons who have received reasonable therapeutic doses of natural concentrates of vitamin K synthetic vitamin K1 or any of the synthetic compounds exhibiting antihemorrhagic activity now available commercially An effect has not been noted on blood pressure respiration, permeability of capillaries or urinary excretion after the administration of any of these compounds It has been observed however, that doses of menadione as large as 180 mgm administered orally to human beings result in vomiting and porphyrinuria Other workers have noted that anemia followed the administration of large doses of vitamin K[139] These huge doses, however are so obviously greater than those employed for therapeutic use that at present it appears safe to continue the therapeutic administration of these synthetic compounds Fieser wisely pointed out that some clinical consideration should be given to the possible conflict or otherwise undesirable characteristics which may be associated with conjugates resulting from administration of menadione He pointed out that the delayed action of the administered material would appear to be subject to considerable uncertainty and that the wide opportunity for transformation of different types would lead one to expect a variability in the response, depending on the manner of administration and the condition of the patient[140 141 14 143]

Diagnosis of Vitamin K Deficiency

The bleeding of patients who have jaundice occurs most frequently after surgical intervention which was calculated to relieve biliary ob

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Bleeding of patients suffering from jaundice occurs most often in the presence of those conditions in which bile is excluded completely from the gastrointestinal tract such as complete biliary obstruction produced by *neoplasms of the pancreas ampulla and gallbladder* Postoperative stricture of the common bile duct is accompanied perhaps by the second highest incidence of bleeding intermittent obstruction caused by the presence of stones comes third Complete external fistulas are relatively rare but often are associated with bleeding Although bleeding *is more* likely to occur in those cases in which bile is excluded completely from the intestine yet the physician must not overlook the fact that bleeding also can occur in the absence of jaundice if the liver has been injured considerably *as the result of chronic cholecystic disease* Although the foregoing facts are somewhat useful for prediction of whether or not a patient will bleed the exceptions are so frequent that rigid clinical rules cannot be devised

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These instances of severe hepatic damage can occur in any disease in which the liver might be involved but most frequently they are seen in cases of cirrhosis of the liver in those in which obstruction or stricture of the common duct has existed over long periods and in those in which

there is acute or subacute atrophy of the liver resulting from some primary disease or associated with acute cholecystitis. Although this group of cases is somewhat small, it is well to remember that it does exist. It is true that repeated doses of vitamin K frequently are necessary to produce the desired effect, but when the physician has doubled or tripled the usual therapeutic dose of vitamin K without producing desired effects, he can be fairly certain that, regardless of the amounts of vitamin K administered, there will be little increase of the prothrombin in the circulating blood.

A deficiency of prothrombin as the cause of bleeding in patients who have various intestinal disturbances is something new in clinical medicine, and although instances of deficiency of prothrombin referable to the effects of intestinal absorption are not encountered often, yet they do comprise a rather distinct group and one which warrants further investigation. The pathological physiology concerned in such cases has been described herein under the section on experimental pathological physiology.

The entire subject of bleeding in the newborn infant has been discussed previously in this chapter.

Obviously knowledge of the conditions in which deficiency of prothrombin may occur is a fundamental requisite for the correct diagnosis of possible deficiency of vitamin K. Although the possibility of hemorrhagic diathesis may be suspected in a particular case, measurement of the prothrombin content of the circulating blood is necessary for accurate diagnosis as well as for evaluation of proper treatment. It must be admitted that present methods for measurement of the content of prothrombin in the circulating blood of patients are subject to considerable error. The decrease in the concentration of prothrombin in the circulating blood of man seems to depend on certain unknown individual factors. Although in certain instances the concentration of prothrombin in the blood apparently depends on the degree of hepatic injury, it certainly does not have any constant relationship to the type of hepatic or biliary disease present.

On the basis of results of the various studies of Smith and his associates[1, 31, 41] it would appear that bleeding among animals in the experimental laboratory occurs when the value for prothrombin becomes less than 20 or 25 per cent of normal and that conversely, so long as the value remains at about 20 or 25 per cent, bleeding does not occur. If this conception is understood, it is easy to see why, in certain cases, bleeding in man may occur postoperatively with little warning. Loss of blood

surgical trauma and the effects of anesthesia and trauma to the liver may *reduce an already depleted supply of prothrombin to a dangerously low level* of these factors mechanical trauma is thought to be the most important The prothrombin clotting time may and frequently does increase with no apparent reason within 6 to 6 hours and with this increase free bleeding may occur without warning and apparently normal coagulable blood may become virtually incoagulable

The prothrombin clotting time of the blood of patients who have jaundice usually increases to some extent for the first 3 or 4 days after surgical operation but it may increase rapidly even as late as the eighteenth postoperative day For this reason the prothrombin clotting time should be determined daily for the first 4 days after operation and then every other day *for at least 8 or 10 days longer* Any increase in the prothrombin clotting time should constitute an indication for the immediate oral or intravenous administration of vitamin K To those patients with a high prothrombin clotting time before surgical treatment *it is perhaps wise to administer the vitamin daily for several days after surgical operation* regardless of the prothrombin clotting time A patient whose blood has a prothrombin clotting time of more than 30 seconds should be prepared with particular care and one whose blood has a prothrombin clotting time of more than 45 seconds must be considered to be a potential bleeder and treated as such

The same important diagnostic points also are applicable in those cases of various intestinal lesions in which a deficiency of prothrombin in the circulating blood may develop

It is equally important to follow if possible the prothrombin clotting time of newborn infants although it is well known that during the first few days *there is a physiological deficiency of prothrombin* This caution is particularly important if any surgical procedure is contemplated during this period of life

Unfortunately the measurement of prothrombin in the circulating *blood does not always give the exact index of the tendency of the patient to bleed* Like any laboratory method this method may not give the clinical information which is always desirable For these reasons prophylactic treatment is much better than treatment after bleeding once occurs

Treatment of Vitamin K Deficiency

No specific remedy for the prevention and control of all instances of bleeding resulting from deficiency of prothrombin has yet been dis

covered The proper administration of vitamin K or related compounds in most instances will be effective, but in addition to obtain the best results all procedures which are known to be of value in the maintenance of adequate hepatic function must be employed Obviously the first objective in treatment of the jaundiced patient who has a tendency to bleed, is to restore continuity of the biliary passages and protection of the hepatic parenchyma

Regardless of the etiological factors involved in the deficiency of prothrombin in man treatment in most instances is essentially the same Since there are now available water-soluble synthetic compounds with

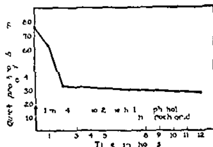


Fig 18

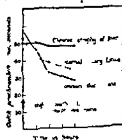


Fig 19

Fig 18 The effect of the intravenous injection of 1 mgm of 4 amino- methyl 1 naphthol hydrochloride on the elevated prothrombin clotting time of a patient who had obstructive jaundice (Butt H R and Snell A M Vitamin K W B Saunders Company Philadelphia 1941)

Fig 19 The effect and rapidity of action of the intravenous injection of mgm of methyl 1,4 naphthoquinone in a case of external biliary fistula and in one of calculus of the common bile duct The figure also shows the failure of this compound to reduce the elevated prothrombin clotting time in a case of chronic atrophy of the liver (Butt H R and Snell A M Vitamin K W B Saunders Company Philadelphia 1941)

vitamin K activity the procedure of giving bile salts to insure proper absorption has been nearly discarded These water soluble synthetic compounds should be administered orally or intravenously in doses of from 1 to 2 mgm daily for several days prior to and after surgical procedures in which deficiency of prothrombin is present or may be expected to develop The rapidity of action of these water soluble compounds with vitamin K activity is shown in Figs 18 and 19

Most investigators interested in this subject suggest that prior to operation in any of these conditions regardless of the concentration of prothrombin in the patient s blood vitamin K in some form should be administered for from 1 to 2 days After operation the concentration of prothrombin in the blood should be followed carefully and vitamin K administered as necessary In instances in which the level of prothrom

bin in the circulating blood is sharply decreased before operation vitamin K should be administered routinely preoperatively and postoperatively for several days and the concentration of prothrombin in the blood should be determined for at least 8 to 10 days thereafter

Some workers[11, 148] recently have felt that the change effected in a particular level of prothrombin by the administration of vitamin K may provide some index as to the nature of the disease being treated with particular reference to intrahepatic and extrahepatic jaundice Data now at hand do not unequivocally establish this fact

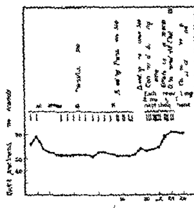


Fig 20 The prothrombin clotting time of a patient who had severe cirrhosis of the liver and who received over a long period various synthetic preparations possessing marked antihemorrhagic activity In spite of these materials the prothrombin clotting time remained elevated This type of case constitutes a failure of vitamin K to correct an elevated prothrombin clotting time (Butt H R and Snell A M Vitamin K W B Saunders Company Philadelphia 1941)

In some patients who have severe acute or chronic hepatic damage hemorrhage develops from deficiency of prothrombin which cannot be corrected by the administration of even large amounts of blood or vitamin K (Fig 20) Recently[149] it was reported that this usually uncontrollable hemorrhagic diathesis could be corrected by the giving of blood from a donor who 24 hours previously had received a large dose of vitamin K Results of our own work at the Mayo Clinic do not support this contention[150]

The discovery and isolation of dicumarol by Link[151] and its clinical application to the prevention of thrombosis[2] have been important steps in clinical medicine As stated previously the administration of dicumarol to human beings results in a decrease in the prothrombin of the blood It is now known by means of the work of several investiga

tors[110 1 3 1 4] that large doses of vitamin K will prevent this decrease in the content of prothrombin in the blood that follows the administration of dicumarol Dicumarol usually is administered to patients, who have pulmonary embolism or thrombophlebitis, or who before surgery give a history of these difficulties The doses employed vary, but as a rule a single dose of 300 mgm of dicumarol is administered on the first day of treatment and 200 mgm is given on the second day, followed by the administration of 200 mgm each day if the prothrombin time is less than 35 seconds (Quick's method of estimation of the prothrombin content) It was observed in one series of 340 patients that 7 per cent were "sensi

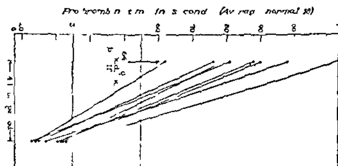


Fig 1 Striking decrease in the prothrombin time after the administration of a single dose of menadione bisulfite to eight patients who had excessive hypoprothrombinemia induced by dicumarol This was the usual response of the condition of such patients (Cromer H E Jr and Barker N W Proceed Staff Meet Mayo Clin 1944 XIX 217)

tive" to dicumarol[110], 'sensitive" meaning that after 1 or 2 doses of dicumarol the prothrombin time increased to 60 seconds or more instead of the usual response of 35 to 55 seconds It was considered that among these 7 per cent bleeding might occur and for this reason a simple and effective method of rapidly lowering the prothrombin time to the neighborhood of 45 seconds or less was needed

The striking effect on the prothrombin time exerted by the administration of large doses of vitamin K is well shown in Fig 21 In these cases a dose of 64 mgm of menadione bisulfite was administered intravenously This dosage is equivalent to 40 mgm of 2 methyl 1,4 naphthoquinone In an occasional case there is no response to these large doses of vitamin K Usually however, there is definite lowering of the prothrombin time limit within 2 hours after vitamin K has been administered and the maximal decrease in the prothrombin time is reached in about 18 hours Clinically these excellent responses to vitamin K indicate that another valuable safety factor has been added to dicumarol therapy

VITAMIN C

History

In 19 8 during studies on tissue respiration systems Szent Gyorgyi[155] secured from adrenal glands a preparation which he subsequently called hexuronic acid This substance was not tested for antiscorbutic activity however at that time In 193 Waugh and King[156] succeeded in the isolation and identification of vitamin C and subsequently it was established that their product was identical with the hexuronic acid obtained by Szent Gyorgyi One year later Reichstein Grussner and Oppenhauer[1] synthesized vitamin C which was named ascorbic acid

Chemistry and Physiology

Ascorbic acid having the formula $C\ H_8O$ falls into the series of hexuronic acid ketones and is closely related to the sugars It is an

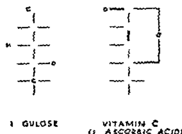


Fig 22 Structural formula 1 gulose and l vitamin C

enediol lactone of an acid similar in configuration to 1 gulose The formulae for both 1 gulose and ascorbic acid are shown in Fig

Ascorbic acid is a crystalline colorless compound which is freely soluble in water and which has a melting point of 19 C The crystals may form pseudo orthorhombic or monoclinic patterns but tend to form rather dense radiation clusters (Fig 3)

The crystals as such are very stable but in aqueous solution rapid oxidation occurs The oxidation reduction reaction of ascorbic acid has been *the subject of much research since 1933 because of the practical impor*tance of possible loss of the vitamin It is now known that many organic compounds including indophenol notably as well as inorganic metallic radicals such as Fe^{+++} and Cu^{++} will oxidize ascorbic acid Aero

the aqueous oxidation of ascorbic acid is accelerated by ordinary as well as ultraviolet light and in the presence of a flavin this reaction is enhanced still more The immediate product of ascorbic acid oxidation is dehydroascorbic acid This product is equally as potent as ascorbic acid

ASCORBIC ACID

Fig 23 Crystalline ascorbic acid

in the treatment of scurvy While at this level the oxidation reduction reaction is reversible, and it is possible to reduce dehydroascorbic acid to ascorbic acid by hydrogen sulfide, cysteine and glutathione The relationship between ascorbic acid and dehydroascorbic acid is clearly shown in Figure 24

DEHYDROASCORBIC ACID   l ASCORBIC ACID (VITAMIN C)

Fig 24 Structural formula of dehydroascorbic acid and l-ascorbic acid.

Dehydroascorbic acid is fairly stable in acidic solutions of pH4 but in solutions of a higher pH oxidation continues to an irreversible level in which there is structural rearrangement with the formation of a potent reducing substance This substance when oxidized gives rise to oxalic acid and l-threonic acid and ascorbic acid thus is destroyed

Both the dextro- and levo rotatory forms of ascorbic acid lend them

selves to synthesis but it is to be remembered that only the levo rotatory form has antiscorbutic properties The dextro rotatory form does not protect against scurvy Several other synthetic substances have been shown to have antiscorbutic activity but to a much lesser degree than *l ascorbic acid*

The important observations of Holst and Frolich[14] on guinea pigs and pigeons gave the first hint that the former animal required an extrinsic supply of vitamin C whereas the latter did not This thought was followed up and it is now understood that of all the animals only the primates and the guinea pig are incapable of synthesizing vitamin C Although *man is incapable* of such synthesis he is capable of storing the supplied vitamin That this is true has been shown by many well controlled experiments and this fact explains the latent period of three to six months or more in the development of scurvy on a vitamin C deficient diet Ascorbic acid is widely distributed in body tissues and fluids *In general it can be said that the younger the tissue and the higher its* metabolic activity the greater will be its ascorbic acid content This has been well shown by the tissue titration studies of Glick and Biskand[12] on normal tissue and similar studies by Musulin and his associates[188] on rapidly growing tumor tissue All of the glandular tissues of the body contain significant amounts of ascorbic acid while the non glandular *body tissues and fluids contain a* lesser amount The *following order* approximates the decreasing concentration of ascorbic acid in the various body tissues and fluids pituitary body corpus luteum adrenal cortex young thymus liver brain testes ovaries spleen thyroid pancreas salivary glands lung kidney intestinal wall heart muscle spinal fluid and blood The pituitary body contains 60 mgm per 100 c c the adrenal gland [illegible]00 mgm per 100 c c muscle mgm per 100 c c and blood plasma 1 mgm per 100 c c

Certain of the glandular secretions and excretory products of the body also contain ascorbic acid Human milk contains four to five times the amount of vitamin C as does cow s milk Thus nature has provided *for the relatively high vitamin C requirements of the nursing infant* who requires about [illegible] to 30 mgm of ascorbic acid a day by establishing the vitamin C content of human milk at 4 to 8 mgm per 100 c c The young calf on the other hand is independent of its mother as far as ascorbic acid is concerned because this animal can synthesize the vitamin *Vitamin C is found normally also in the urine feces* and sweat By far the greatest amount is excreted in the urine the total amount excreted a day being 13 to 40 mgm Vitamin C is a so-called threshold sub

stance with a critical level of excretion at approximately 1 4 mgm per 100 c c of plasma The urinary excretion of the vitamin is enhanced by many drugs such as ammonium chloride, atropine, sodium bicarbonate the salicylates and the barbiturates, while insulin results in a lowered excretion An additional 6 to 10 mgm is excreted in the feces, and another 0 55 to 0 64 mgm per 100 c c is excreted in the sweat These excretion levels obviously depend upon dietary intake and increased destruction or demand for the vitamin

The body physiological economy of vitamin C is reflected in the concentration of the vitamin in these various excretions fluids and tissues Should the extrinsic supply of ascorbic acid be restricted, there is observed a disappearance of vitamin C from these elements in an order inversely proportional to their ascorbic acid content in the physiological state Thus, urinary excretion of vitamin C ceases long before the plasma level is significantly reduced In the same manner the plasma level may be zero, while the white cell-platelet layer is normal This retrograde depletion so to speak continues until finally the pituitary body is depleted of the vitamin The converse is true when a primate or guinea pig so depleted of vitamin C then is saturated with it The tissues first take their share, then the body fluids and lastly ascorbic acid appears in the body excretions The amount of the vitamin required to induce saturation thus is a very rough estimate of the state of vitamin C nutrition Crandon and Lund[161] and more recently Pijoan and Lozner[16] have conducted experimental studies in human scurvy which bear out this concept One of the latter authors showed that even though the urinary excretion of vitamin C had long since ceased and the plasma level was 0 0 to 0 mgm for twenty months the white cell-platelet layer contained 15 mgm per 100 c c and clinical scurvy did not develop These studies have been confirmed by many investigators and there is little doubt but that the vitamin C concentration in the white cell-platelet layer of centrifuged blood correlates much better with the clinical findings than does the vitamin C concentration elsewhere It should be remembered, however, that in the normal physiological state there is an excretion of vitamin C in the urine and that there is a concentration of ascorbic acid in the blood plasma of 1 2 mg per 100 c c A deviation from these findings is not physiological and should prompt the physician to suspect a deficiency of vitamin C and guide him to an investigation of the dietary and the application of the vitamin C saturation test

The physiological functions of vitamin C include a long list However the most clearly defined of these is the formation of reticulum and

collagen so as to maintain the integrity of the intercellular substance[1] It is believed that vitamin C may be the sole factor which is responsible for the cementing together of the reticulum by a translucent matrix to form collagen in between the cells of tissue Vitamin C exerts its efforts only on tissue of mesenchymal origin The precise mechanism of this function is unknown

Vitamin C is concerned further with the over all growth of the organism It has been shown to be a powerful growth stimulant in the young plant embryos and it is reasonable to assume that it has such a function in man Growth and development studies are such long term problems that only a few such observations have been made under controlled conditions in man and in the experimental animal

As to the function of vitamin C as a hematopoietic substance there is considerable doubt It has not been shown conclusively that deficiency of ascorbic acid itself is a direct cause of the anemia seen in association with scurvy It is quite possible that many other factors are at work as discussed in the section on Pathological Physiology

Accumulating evidence is appearing that vitamin C may play a role in resistance to infection and certain toxins King and Menten[164] and Sigal and King[16] found that guinea pigs in the pre scorbutic state were more sensitive to tissue injury by diphtheria toxin than were normal ones and that the metabolism of these animals was lowered significantly The latter is probably a natural defense mechanism to conserve the vitamin C stores The authors have observed that resistance to disease is lowered significantly in general nutritive failure but how much vitamin C is directly responsible for this is not known The function of vitamin C in certain enzyme systems still is without proof or even general agreement That such a function may exist is not too unlikely but this subject is so imperfectly understood that at present no concrete statements can be made

It is evident that there is little precise knowledge concerning the physiology and metabolism of vitamin C Studies in vitro show poor correlation with observations in vivo A long wide vista may lie before science with the recent advent of the capability of marking carbon atoms By this means it may be possible to follow ascorbic acid through the body as it performs its functions in vivo

Pathological Physiology

Deficiency in vitamin C expresses itself most characteristically in the development of scurvy The pathological physiology of vitamin C can

be understood best from a discussion of the pathological physiology of scurvy A clearer understanding of the pathological physiology of scurvy is gained, if one recalls that the primary and most clearly defined function of vitamin C is the maintenance of the integrity of the intercellular substance A lack or a deficiency of vitamin C results in an impairment of this function with a subsequent manifestation of the symptoms and signs of the state we recognize as scurvy A deficiency of vitamin C may result from one or a combination of any of the several following factors, (1) a deficient dietary intake ( ) impaired intestinal absorption (3) increased body requirements for the vitamin (4) faulty assimilation (5) faulty utilization and (6) increased destruction in vivo of the vitamin

A new era in the pathogenesis of scurvy was inaugurated by S B Wolbach and his associates[165, 166, 16] from 1926 to 1937, when they showed that the intercellular substance was seriously affected in scurvy In their scorbutic animals the ground substance and fibroblasts were present but there was no reticulum nor collagen present Such defective intercellular material has been found in connective tissue bone and teeth Within twenty-four hours after the administration of vitamin C to such scorbutic animals whole bundles of collagen were formed Although the capillaries are believed to be involved both from the clinical and embryonic points of view, no such morphological lesions have been found

In the formation of bone and cartilage the intercellular substance is of major importance The lesions produced in these structures due to lack of vitamin C are similar to the scorbutic changes in other parts of the body and like them are due to a failure to form intercellular substance The anatomical location of these lesions depends to a large extent on two factors, growth and stress This explains why bony lesions and hematomas are seen so commonly in the child These factors explain further the occurrence of petechiae in either usual or unusual locations The frequently cited example of the scorbutic blacksmith who had many petechiae over the shoulders and arms thus is given an explanation

Gross changes in bone in vitamin C deficiency are seen most commonly at the costochondral junctions the distal end of the femur the proximal end of the tibia and of the humerus and the wrist In the scorbutic state formation of cartilage and bone matrices soon ceases The osteoblasts are surrounded by liquid and no collagen is to be seen This results in the rarefied area at the ends of the diaphysis seen in x rays (Fig 25) The Germans aptly termed this appearance 'Gerustmark frame work marrow as the strands of apparent connective tissue seem to be

surrounded by a liquid The osteoblasts revert to their prototype in scurvy and form a fibrous rather than a bony union between the diaphysis and the epiphysis thus permitting false motion sometimes in these areas The cortex of the bone rarefies and becomes very thin so that



Fig 5 X ray of long bones in scurvy

fractures from trivial traumata occur The periosteum is only loosely attached to the bone and eventually becomes stripped from the shell like cortex Because of the unyielding nature of the cortex subperiosteal hemorrhages occur frequently Such hemorrhages further strip the periosteum giving the picture so characteristic of the scorbutic state

The response to ascorbic acid is dramatic. Within a day this sickly process is reversed and bundles of collagen can be seen. Osteoid material appears in a few hours around the osteoblasts with the formation of trabeculae and the cessation of hemorrhages from the fragile capillaries. In short, normal bone formation starts again. Vitamin C is also essential for the callus formation necessary for the healing of fractured bones. This explains the observations made in Lind's time of the old healed fractures breaking down when sailors developed scurvy.

Faulty formation of intercellular substance in connective tissue is of practical importance in wound healing. It has been widely observed that in the scorbutic person minor abrasions and wounds heal very slowly. Crandon[161] studied and finally settled this problem by his well controlled experiments on himself. For a period of 6 months he restricted himself to a vitamin C-free diet, supplemented by all the other known vitamins. At the end of the first 3 months on such a diet a wound was made on his back. This wound healed well, and histological examination showed ample intercellular substance and capillary formation. After he had been on the restricted diet for 6 months and had had clinical scurvy for 3 weeks, a wound similar to the first was made. The skin healed but the wound beneath did not. Unorganized blood clots filled the wound and histological study of the tissue showed the same lack of intercellular substance and capillary formation as was found by Wolbach in wounds of scorbutic guinea pigs. Crandon then received an intramuscular injection of 1,000 mgm. of ascorbic acid. A biopsy specimen taken from the wound 10 days later showed good healing and ample intercellular substance. This observation shows that vitamin C is an important factor in the healing of a wound but the physician must not lose sight of the fact that wound healing is dependent on many other factors.

The lesions appearing in the mouth in vitamin C deficiency are more difficult to explain. The gingiva is involved only when teeth are present, an observation that still is without explanation. Hess[178] was of the opinion that infection played a prominent role in the gingival lesions, but one can observe gingival signs of scurvy before infection supervenes. Certainly there is an increase in the number of capillaries present, resulting in congestion and swelling of the gums. These vessels are of poor quality and give rise to frequent hemorrhage. The intercellular substance of the tissue itself is defective and the gingiva becomes easily infected and subsequently breaks down to become ulcerated and even gangrenous. The teeth themselves undergo much the same change as does bone, the main defect occurring in the dentine. There is resorption of normal dentine

beginning along Tomes canals and formation of an inferior type of *osteodentin or of pulpstone which results from metaplasia of the dentin forming cells* The pulp becomes hyperemic and edematous and atrophy and degeneration of the odontoblast layer follow There is no convincing evidence that dental decay in man is due to ascorbic acid deficiency Falling out of the teeth in ascorbic acid deficiency is the direct result of thinning of the alveolar bone such as occurs in other bones There still is a conspicuous lack of precise knowledge as to the relationship between vitamin C and gingival and tooth disease in man

That *the petechial and ecchymotic hemorrhages of the scorbutic* state occur cannot be denied Stress plays an important role in their location and such lesions are found where a vessel rides over a bony prominence or where a belt has been pulled tight The integrity of the capillary wall has been studied and morphological changes are wanting A cement substance is believed to fuse together the endothelium of the capillaries However connective tissue also surrounds the capillary and very thin collagenous fibers ensheath the endothelium It is still undecided whether *the connective tissue sheath or the endothelial cement* substance is affected in scurvy The relationship of vitamin C to so called capillary resistance is indeed a knotty problem Crandon[10] found that even though he had the perifollicular hemorrhages of scurvy over his legs the positive pressure test done in the arm was negative

With the isolation and subsequent synthesis of vitamin C came a volume of reports that the newly available vitamin would cure many of the nonscorbutic hemorrhagic diseases All these claims have been dispelled and *it is now established that vitamin C will have a favorable effect only on the hemorrhages of scorbutic origin* Within the past twelve years much investigation has been carried out on the permeability of capillaries Szent Györgyi isolated a substance which he called citrin at first and later vitamin P He believed this new vitamin controlled capillary permeability and resistance and that it was responsible for the petechial hemorrhages seen in scurvy but two years later he was unable to obtain similar results Much has been done since then and the reports are conflicting Recently Shanno[16] reported on the use of rutin for the treatment of increased capillary fragility He points out that citrin or vitamin P is an impure mixture *of two flavone glucosides* hesperidin and eriodictyol *These two substances he claims are physiologically inert* and that possibly the active principle in citrin was rutin The authors have studied the relationship of abnormal capillary fragility ascorbic acid deficiency vitamin P and rutin for years and have not found in their

studies a sufficiently clear relationship to warrant reporting their results

In 1930 Mettier, Minot and Townsend[110] stated that anemia is found commonly in adults with chronic vitamin C deficiency They concluded from their studies that this anemia responded specifically when orange juice was administered but did not respond to iron or purified liver extract They showed that the erythrocytes were normocytic, normochromic or moderately macrocytic hyperchromic in contrast to previous teachings that the cells generally were hypochromic They found the bone marrow to be moderately hyperplastic and normoblastic prior to therapy After orange juice was administered, they noted an increase in cellularity of the marrow due principally to an increase in normoblasts

Since 1930 numerous observers have reported hematological studies on persons with scurvy Much of this work seems to indicate that scurvy and anemia do not necessarily coexist, that experimental vitamin C lack does not interfere with blood formation and that patients with naturally occurring scurvy and anemia show erythrocyte and hemoglobin regeneration while on a vitamin C-free but otherwise adequate diet The bone marrow has been described variously as hyperplastic with normoblastic maturation arrest as hypoplastic and as megaloblastic In short the inference is that vitamin C is not essential for normal hematopoiesis and that hemorrhage lack of iron and some unknown vitamin B complex or other deficiency state account for scorbutic anemia The experiment of Crandon mentioned above is worthy of note for in spite of blood loss incurred in making various blood determinations he did not develop anemia The hemoglobin started to fall in the third month but returned to normal values following the ingestion of ferrous sulphate daily More recently Lozner[111] has shown that iron alone caused hemoglobin regeneration in patients with vitamin C deficiency It is interesting that Wolbach[112] found in long continued partial vitamin C deficiency in the guinea pig that large regions of bone marrow became devoid of blood forming cells and the seat of a deposit of amyloid like material He believed that the anemia associated with the scorbutic state in the guinea pig was a secondary phenomenon No such bone marrow deposits have been found in man however Hence to state it mildly, one must say the evidence in the human being is conflicting

The recent studies of Vilter Woolford and Spies[113] throw light on this problem They studied carefully 19 cases of severe scurvy admitted to a large municipal hospital Several features worthy of special emphasis are pointed out by these investigators The general appearance of

patients with severe scurvy is distinctive Stasis cyanosis in the extremities sallow dirty gray cadaveric skin color somnolence lethargy and hypotension appear insidiously and are the prodromata of peripheral vascular collapse which may occur suddenly without further warning Cheyne Stokes type of respiration occurs particularly in patients with arteriosclerotic cerebrovascular disease and anemia All of these vasomotor abnormalities disappear within from 4 to 36 hours after the oral or parenteral administration of adequate amounts of vitamin C Although

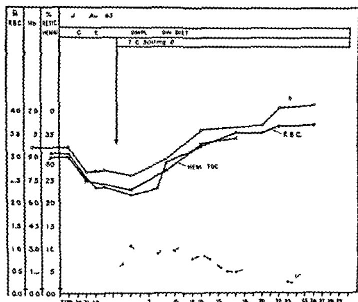


Fig 6 Decline in erythrocyte and hemoglobin in severe scurvy as clinical course grew worse prior to vitamin C therapy (from Jour Lab and Clin Med 1946 XXXI 609)

the exact mechanism responsible for these changes is unknown it should be noted that in guinea pigs and rats a direct relationship has been reported to exist between the vitamin C stored in the adrenals and the synthesis of adrenocortical steroids

The hematological data (Fig 6) gathered from our patients with anemia while they are subsisting on diets very low in vitamin C and low in the vitamins of the B complex corroborate many of the original observations of Mettier Minot and Townsend using orange juice Nine of the critically deficient patients either did not improve clinically or

hematologically or became more anemic and debilitated on this diet Striking hematological and clinical recovery occurred after vitamin C alone was added to the experimental regime, much the same effect previously reported for orange juice

The authors have found other patients with mild moderate or severe scurvy and with no anemia In fact a normal blood picture has been found in 12 ambulatory patients with scurvy who have entered the Nutrition Clinic Hillman Hospital Further observations from this clinic indicate that many nutritionally deficient persons repeatedly have had negative tests for vitamin C in the plasma for as long as 5 consecutive years and yet they did not develop clinical scurvy or anemia The factors which cause the development of anemia in some persons with scurvy but not in others are not understood Certain considerations, however help explain this variation in patients In the normal course of events deficiency diseases seldom occur as single entities Deficient diets seldom are deficient in a single essential factor

A patient with severe vitamin C depletion may have no anemia until additional strain is placed on the bone marrow by a deficiency of protein iron or other unknown factors which may be necessary for normal hematopoiesis Yet after the anemia has developed the deficiency of the latter factors may not be serious enough to prevent a remission when large amounts of ascorbic acid are administered In many deficient persons bed rest which reduces metabolic requirement for all essential nutrients may be sufficient therapy to produce a clinical and hematological remission Depending on the interplay of multiple factors morphological differences in blood and bone marrow and varied therapeutic responses may occur readily in patients with scurvy and other deficiency states For these reasons observations on patients who were critically ill with scurvy anemia and other deficiency diseases of long standing cannot be compared satisfactorily with data on human subjects in whom a single deficiency state scurvy has been produced experimentally without the occurrence of anemia

SYMPTOMATOLOGY

As for its pathological physiology the symptomatology of vitamin C deficiency may be described by a summary of the symptoms of scurvy Scurvy is encountered most frequently in the very young and the very old but no sex race or age group is exempt There are certain points of difference in the scurvy seen in the young infant and that seen in the

adult For sake of clarity, therefore an arbitrary distinction is made and the symptomatology of these two age groups is discussed separately The etiology and general pathology are the same however the manifestations in the one instance occurring in immature, rapidly growing tissue and in the other instance in mature slow growing tissue

Infantile Scurvy

The classical picture of acute florid infantile scurvy is the most widely known variety yet it is a picture we should not allow to be seen today In this neglected almost terminal state the child cries out as its bed is approached The afflicted infant lies motionless on its back with one or both thighs everted and flexed on the abdomen The thighs are swollen and severely tender To touch the child anywhere results in a cry of both pain and horror This type presents a striking picture and is not easily forgotten This form of scurvy is not the most common nor is the practicing physician likely to see it The most common form of the disease generally *is encountered in the last half of the first year* The mother s presenting complaint may be that her child is not gaining weight properly or that he is unusually irritable or lethargic and does not eat well The infant appears pale and sallow and the only physical abnormality may be very questionable tenderness over the distal end of the femur The diagnosis of scurvy in this instance usually is based on the response to specific therapy This is the so-called latent form of scurvy If treatment is not instituted manifest scurvy develops Beading of the ribs may occur and thus complicate the picture by suggesting a *diagnosis of rickets However vitamin D fails to correct the defect* Later subperiosteal hemorrhages may result from trauma so trivial as not to be remembered Such hemorrhages may occur in the adult but it is a rare finding The resultant swellings are very tender and usually will involve the lower end of the femur and the proximal end of the tibia although they may involve other bones Such hemorrhages are seen easily in the x ray In addition to subperiosteal hemorrhages there may be hemorrhages into the soft tissue The hair follicles and sweat glands are particularly susceptible Again stress is an important factor in the *location of these petechiae and ecchymoses In many instances the diaper* is responsible for the production of such lesions on the inner aspect of the thigh Gross hemorrhage may occur elsewhere as the disease progresses giving rise to epistaxis hemoptysis bloody diarrhea and occa

sionally, hemothorax When such hemorrhages occur in abdominal organs or in the brain, confusing and alarming symptoms ensue

The lesions of the gums may be so mild initially as to be overlooked They are seen only when teeth are present The gums show a very mild, peridental hemorrhage or merely a border of increased redness about the tooth Later the gums become swollen and purple and as progression occurs, infection is added, and the ulcerated, fetid gum of the acute case is seen

In addition the infant may present early slight elevations of temperature which become more marked as the disease continues A similar slight increase in the respiratory rate may occur as a result of mild pain on motion of the costochondral junctions The respiration thus may be shallow and more rapid than normal

Adult Scurvy

The initial symptoms of vitamin C deficiency in the adult are as ill defined as they are in the child After a long period of deficiency of vitamin C the adult will develop symptoms of lassitude, irritability, easy fatigability and insidious weight loss Vague aches and pains in the muscles and about the joints appear so as to stimulate "rheumatism" The face is pale and sometimes bloated the skin being a dirty gray, ashen color There may be hypotension and stasis cyanosis

In the absence of adequate therapy the symptoms and signs become more marked The muscle and joint pains become severe and are the result of hemorrhage into and around these structures Large ecchymoses are frequent, and their color varies greatly The more recent ones are red, while the older ones are blue brown or green In addition the well known perifollicular petechiae become evident Again these symptoms and signs are dependent on stress and lines of force The petechial hemorrhages may occur almost anywhere in the skin but are more common over the lower extremities Subungual hemorrhages and splinter hemorrhages may occur Gross hemorrhage may result in epistaxis and other manifestations as listed under infantile scurvy Subconjunctional hemorrhages are seen occasionally

The gum lesions follow the same pattern as in infantile scurvy In some instances the gums become so swollen and congested as to cover the teeth completely thereby making mastication a very painful procedure The teeth become loose and eventually may fall out

Anemia is not uncommon in adult scurvy and the complaints referable to this state are the same as for any normocytic anemia The palpitation dyspnea and cardiac dilatation sometimes seen are most likely the result of the lowered erythrocyte count and consequent anoxemia

As one follows the sequence of events from early to late scurvy it becomes apparent that a correct and early diagnosis is very important in view of the fact that the disorder is not self limited and that we possess specific remedies for it The diagnosis may be difficult for those who have gleaned their information merely from the textbooks Some persons with scurvy have been treated again and again for rheumatism Surgeons must be alert for signs of ascorbic acid deficiency when they perform an operation for bone tumor or osteomyelitis If the treatment is inadequate the cure may be incomplete and the disease persist for years At best it probably takes months or years before the tissues return to anything like their normal state after treatment

Diagnosis

The diagnosis of vitamin C deficiency in the form of manifest scurvy in the adult or in the infant is not difficult for the well trained physician A careful physical examination and a history of an inadequate intake of vitamin C aid in making a tentative diagnosis and x ray and certain laboratory tests may add confirmatory evidence

The fundamental hemorrhagic tendency which results from loss of tensile strength of connective tissue because of alteration in or lack of intercellular substance may appear in any part of the body Hemorrhages are most likely to occur at sites of stress due to injury motion growth or infection Hemorrhages of the gums are common and painful In the extremities where capillary pressure is high and at the site of the hair follicles petechiae may appear Ecchymoses are common Hemorrhages may occur at the joints and cause considerable pain This may result in hyperesthesia on motion which in infants causes fretfulness and a motionless frog like position of the lower limbs In the brain intestine or kidney gross or microscopical hemorrhages may occur

Skeletal lesions lead to diagnostic x ray findings In the infant or child such lesions are likely to occur at the growing costochondral junctions and at the ends of the long bones causing a characteristic shelf like costochondral beading The x ray shows a zone of diminished density which is known as the scorbutic lattice The defective calcification at

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blood dyscrasia Even in severe scurvy a negative capillary test sometimes occurs so that this test, in itself cannot be considered as diagnostic of scurvy

If a diagnosis of scurvy is in doubt, a therapeutic test is recommended 50 mgm of ascorbic acid should be administered parenterally while the patient is kept on his usual routine Then he should be watched carefully for any alteration of symptoms

Prevention and Treatment

That fresh fruits and vegetables are of great value in the protection against and in the cure of vitamin C deficiency is every day knowledge Vitamin C is present in all living tissue but fresh fruits and plants are the best sources (Fig 27) Rose hips haws currants strawberries cabbage tomatoes and the citrus fruits are the richest sources Potatoes spinach and turnips are good sources Many people depend on the potato for their quota of ascorbic acid by eating it daily in large amounts One half pound of potatoes supplies about 30 mgm of ascorbic acid an amount which is considered adequate to protect against scurvy The amount of vitamin C in fresh fruits or vegetables varies widely depending on maturity time of picking variety season and soil

Beginning in the second week of life the infant should be given 1 to 2 teaspoons of fresh orange juice daily or 25 mgm of ascorbic acid The amount should be increased to 2 ounces by the time the child is 3 months of age and to 3 ounces by the age of 5 months Other citrus fruits may be substituted for oranges but when tomato juice is used large amounts should be given If fruit juices are not tolerated 25 to 50 mgm of ascorbic acid should be given daily At least 3 ounces of orange juice comparable amounts of citrus fruits or tomato juice or 50 to 100 mgm of ascorbic acid should be taken daily by the average adult Larger amounts of these materials are indicated during pregnancy and lactation

Scurvy which is due to vitamin C deficiency may be treated by administering ascorbic acid orally or by injection Parenteral administration is about twice as effective per unit of weight as is oral administration and is indicated always in stupor or coma or where there is difficulty in absorption from the alimentary tract Ascorbic acid is readily soluble and may be added to sterile saline solution or to 5 per cent glucose solution Because it is too strong an acid to be injected intramuscularly sodium bicarbonate should be added as a neutralizing agent to solutions for intramuscular injection For intravenous injections neutralization is

this zone predisposes to fracture with subperiosteal hemorrhage and slipping of the epiphysis Cessation of growth allows an intensification of calcification at the zone of preparatory calcification at the epiphyseal ends of the long bones and at the periphery of the epiphyseal centers of ossification In the x-rays these appear as 'the white lines of Frankel Eventually thinning of the cortex and trabeculae of the shaft gives the bones a ground glass' appearance in the x-ray In the infant or in the adult these clinical or x ray signs of scurvy become apparent only after some three months or more on a deficient diet

Some physicians are misinformed as to the value of laboratory tests in making a diagnosis of scurvy as an evidence of vitamin deficiency Among investigators there is considerable difference of opinion as to the value of the urinary excretion test and the measurement of the whole blood or plasma levels of ascorbic acid in determining the state of ascorbic acid nutrition The authors use these laboratory tests only to gain more information never to make a diagnosis It is certain however, that the tissues are not adequately filled with vitamin C for months before clinical evidence of scurvy appears Following the administration of a parenteral test dose of ascorbic acid normal persons excrete approximately 60 per cent of the total 24 hour excretion during the first 3 to 5 hours whereas persons deficient in ascorbic acid excrete much less Youmans[14] is of the opinion that plasma values below 0.4 mgm per 100 c c represent a state of deficiency in which clinical signs may appear Crandon Lund and Dill[17] found that low or even zero findings may not be critically dangerous unless maintained over a long period of time We have observed patients who have had zero values for over 5 years without the appearance of a diagnostic lesion of scurvy Nevertheless we are of the opinion that important information in respect to vitamin C metabolism can be gained by determination of the ascorbic acid content of the plasma Harris Hielman Jensen and Spies[16] have conducted extensive studies on normal persons and on patients in the Nutrition Clinic in Birmingham They found that the ascorbic acid of the plasma of the patients was 51 per cent of that of the normal persons The authors believe that a level of ascorbic acid below 0 4 mgm per 100 c c indicates that the reserve supply of ascorbic acid is at a danger point that levels of from 0 4 to 0 7 mgm per 100 c c indicate that the reserve supply is low, and that values ranging from 0 7 to 1 2 mgm per 100 c c indicate an adequate reserve supply

A positive capillary resistance test suggests a depletion of vitamin C, but false positives frequently occur in the presence of severe anemia or

dietaries of children with deficiency diseases and the allowance recommended the degree of deficiency of other essential nutrients which remain after the deficiency of vitamin C is shown clearly

The other vitamin deficiencies associated with many cases of scurvy should be searched for and treated An excellent diet should be given always and additional specific therapy should be given also and continued until all evidence of vitamin C deficiency has disappeared When

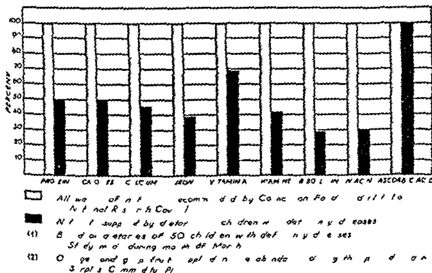


Fig 8 Nutrients supplied by dietaries of children with deficiency diseases contrasted to recommended allowances of nutrients

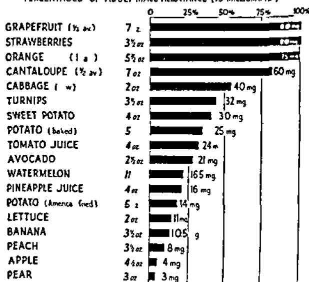
gingivitis is present mouth washes should be prescribed and splints for the legs should be applied when indicated

The response to adequate therapy with ascorbic acid is dramatic Bone tenderness decreases purpura begins to fade gums improve appetite increases and loss of apprehension occurs within 24 hours after sufficient amounts are administered by the parenteral route A similar striking improvement follows adequate oral therapy The general treatment should be directed toward restoring the patient to a state of perfect nutrition

unnecessary It should be mentioned that ascorbic acid is excreted more rapidly following intravenous than intramuscular injection Ascorbic

FOODS AS SOURCES OF
ASCORBIC ACID
(VITAMIN C)

In addition to citrus fruits and tomatoes many common fruits and vegetables supply significant amounts of ascorbic acid, especially if eaten raw This vitamin is readily destroyed by heat and it is extracted by water



Council on Foods and Nutrition, American Medical Association and Food and Nutrition Board National Research Council

FIG 27 Foods as sources of ascorbic acid (Vitamin C)

acid has a very low toxicity The authors frequently have injected 1,000 mgm or given 5 000 mgm by mouth without any ill effects It is very important to continue intensive therapy until all the lesions are healed and then give a daily maintenance dose of 50 to 100 mgm orally

It should be emphasized that the present knowledge is so meager that a precise statement of what constitutes proper dosage is not practicable Since vitamin C deficiency is frequently a part of mixed deficiency diseases, it is not enough to insure an adequate intake of vitamin C alone In Figure 28 showing the contrast between the nutrients supplied by

Eijkman, Funk, Vedder, Grijns, Williams, Peters, Cline, Westenbrink, Jansen, Seidell, Sinclair, Waterman and many others are held in reverent esteem as contributors of important knowledge of vitamin B_1

Chemistry and Physiology

Vitamin B_1 (thiamine) is a white crystalline compound (Fig 29) which is prepared synthetically as the hydrochloride (Fig 30) The properties of the natural and the synthetic compound are identical The

Fig 30 Structural formula of thiamine chloride hydrochloride

hydrochloride melts at 248 to 250° C and is very soluble in water It is stable at 100° C in acid solution but is destroyed at 100° C in neutral or alkaline solution

Vitamin B_1 is important in tissue oxidation of carbohydrate compounds Apparently it acts as a compound capable of reversing oxidation and reduction Vitamin B_1 represents the reduced form and can be oxidized to a disulfide the oxidation occurring under physiological conditions The disulfide shows full vitamin activity The disulfide can be reduced to the thiol form by hydrogen hydrogen sulfide glutathione and other substances

PHOSPHORIC ACID ESTER OF THIAMINE (COCARBOXYLASE)

Fig 31 Structural formula of phosphoric acid ester of thiamine (cocarboxylase)

Yeast contains a specific catalyst called carboxylase which decarboxylates pyruvic acid as is shown below

$$CH_3CO\ COOH \xrightarrow{\text{Vitamin } B_1\text{—pyrophosphate}} CH_3\ CHO + CO$$

VITAMIN B_1 (THIAMINE)

History

The modern era of the study of vitamin B_1 was initiated by Eijkman[177], who induced polyneuritic symptoms in fowls fed a diet of polished rice. When they were fed unpolished rice they did not develop the disease and rice polishings relieved the afflicted birds. Grijns[178] concluded that human beriberi and avian polyneuritis resulted from a lack of the same substances in the rice bran but physicians and other scientists still were not impressed. It was not until Fletcher[179] and Fraser and Stanton[180] established the fact that unpolished grain would aid in pre-



Fig. 9. Crystalline thiamine chloride hydrochloride (courtesy of Merck and Co.)

venting beriberi that serious consideration was given to these theories. Funk[181] made a concentrate of the active principle in rice polishings and thought he had isolated the antiberiberi vitamin. His coinage of the word "vitamine" was very fortunate in that it caught the imagination of many for the first time. In 1913 Vedder and Williams[182] concentrated the factor from rice polishings and showed that it was dialyzable and absorbed it on charcoal. Seidell[183] made the important contribution that it could be adsorbed on fuller's earth and removed with alkali, and Peters[184] introduced still more refinements. A milestone in the isolation was passed in 1926 when Jansen and Donath[185] successfully isolated the pure vitamin for the first time. The final word in the chapter was written brilliantly by Williams and his school[186] when they synthesized the vitamin in 1936. Throughout the scientific world the names of Takaki,

brain The greater part of the total body store is in the liver and muscles On a diet deficient in thiamine the amount stored declines rapidly at first then more slowly and the last traces are held most persistently Much work is being done on the excretion of thiamine and there is a great need to know *more of its distribution in tissues*

An excess intake of thiamine is wasted chiefly by excretion from or destruction in the body Only a small percentage of the intake from a diet rich in vitamin B1 is excreted in the urine but the kidney concentrates it from the plasma to a marked degree twenty times or more The fecal output is relatively small but fairly constant At the present time our knowledge of the importance of thiamine excretion in the sweat rests on evidence too slender to be interpreted We can be certain that in human beings and in animals the total amount excreted decreases with restriction of the vitamin in the diet

Platt and Lu[155] have shown that the bisulfite binding power of the blood is increased in human beings with thiamine deficiency This determination is not entirely specific for pyruvic acid since any aldehyde or ketone group also would give positive tests Nevertheless in vitamin B1 deficiency a part of the bisulfite binding substance has been identified definitely as pyruvic acid In addition to lactic acid methyl glyoxal has been found in the blood of persons with beriberi Glyoxal is pyruvic aldehyde and is a stage of oxidation of the terminal carbon atom whereas lactic acid is the result of incomplete oxidation of the central carbon atom

Lewy Spies and Aring[157] gave by injection 50 mgm of synthetic cocarboxylase to patients with nutritional peripheral neuritis and observed that the under excitable nerve muscle apparatus was restored to normal excitability within one to four hours This finding indicates that a great number of the nerve fibers were anatomically intact although they were unable to respond properly due to the altered metabolism In all the patients who received only a single injection and who continued to eat a diet deficient in thiamine the nerve muscle mechanism returned to its poorly functioning state within a few days Another injection of either cocarboxylase or thiamine again relieved these patients *The more severely affected muscles remained underexcitable following* a single injection which probably means that too many of their fibers were morphologically damaged to permit prompt restoration of function These observations support the concept that the early stage of the clinical deficiency state is characterized by a biochemical rather than an anatomical lesion These investigators studied the thiamine excretion in

The coenzyme of this reaction is the phosphoric acid enzyme of thiamine cocarboxylase It has been synthesized enzymatically and by chemical methods, and Lohman and Schuster[18] proved that it was the pyrophosphate of vitamin B_1 The action of vitamin B_1 in the body is due partly or mainly to the action of cocarboxylase (Fig 31) The liver transforms much of the vitamin B_1 into cocarboxylase and it also can hydrolyze cocarboxylase to form vitamin B_1 The kidney phosphorylates thiamine

It appears then that vitamin B_1 in the body acts as an acceptor for such substances as adenosin triphosphoric acid The carboxylase system consists of a specific protein and the coenzyme, the cocarboxylase, and the metal ions Manganese, magnesium and iron are stimulants, and zinc calcium, nickel and cobalt retard in small concentration Presumably the metal element in the enzyme acts as a cement substance binding protein to cocarboxylase The chemical reactions of cocarboxylase resemble closely those of vitamin B_1 The molecular weight of the protein particle of cocarboxylase is not known, but it is estimated to be 150 000 The vitamin action occurs as a result of the specific structure of the molecule The different salts of the vitamin have a corresponding activity Structural alterations are followed by a disappearance of vitamin actions The pyrimidine ring the thiazole ring and the methylene bridge between them an unsubstituted amino-group in 4 position of the pyrimidine ring the 5 hydroxy-alkyl-group and free -4-position in the thiazole nucleus are necessary for the vitamin action

Vitamin B_1 is widely distributed in raw foodstuffs The richest sources are whole cereals yeast and pork Yet even these foods do not contain a great abundance of the vitamin During the preparation of food for consumption much of the vitamin is lost Heat destroys some and since the vitamin is water-soluble considerable is lost in discarding the water in which food is cooked Discarding the bones of meat and the peelings and cores of fruit also accounts for some of the loss which occurs during the preparation of food Vegetables are not rich in thiamine, but they are important sources because they are inexpensive In the average diet approximately 25 per cent of the total thiamine is obtained from cereals or cereal products Unenriched white flour contains little thiamine as contrasted with whole wheat flour, only about one tenth of the amount originally present in the whole wheat Legumes nuts sugar cane molasses and whole cornmeal are all rich in vitamin B_1

Man cannot synthesize thiamine, nor can he store it to any great degree The highest concentration is in the liver, kidney, heart and

brain The greater part of the total body store is in the liver and muscles On a diet deficient in thiamine the amount stored declines rapidly at first then more slowly and the last traces are held most persistently Much work is being done on the excretion of thiamine, and there is a great need to know more of its distribution in tissues

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the urine of these patients It was learned that the patients retained much more of the injected cocarboxylase than did the normal controls The bisulfite binding substance decreased in the patients who retained the cocarboxylase and the same patients showed electrical and clinical improvement, which suggests an association between these factors It may be well to stress that the degree of neuropathy seen in the south of the United States, where Lewy, Spies and Aring were working, cannot be compared to the severe forms of neuropathy seen in many clinics in association with long standing and heavy addiction to alcohol

Vitamin B_1 plays an important part in carbohydrate metabolism Glucose is not oxidized directly in the body but is transformed into CO and H O in a number of stages Two of the intermediate products are lactic acid and pyruvic acid It is thought that vitamin B_1 in its phosphorylated form cocarboxylase acts as a specific catalyst in breaking down pyruvic acid Pyruvic acid and lactic acid are increased in the blood and in the urine of vitamin B_1 deficient patients and animals Peters[190] has shown that the brains and kidneys of avitaminotic pigeons have a diminished oxygen uptake Himwich Spies Fazekas and Nesin[11] have shown that the neurological lesions probably are due to an inability of the vitamin B_1 deficient patient to oxidize glucose efficiently These investigators were concerned about the cerebral metabolism of patients who had pellagra with or without clinical vitamin B_1 deficiency They reasoned that because the brain oxidized carbohydrate chiefly any alteration in carbohydrate metabolism resulting from a deficiency of thiamine should be observed more readily in the brain than in any other organ which was capable of oxidizing fat as well as carbohydrate The carbohydrate metabolism was studied by measuring the differences between the oxygen glucose and lactic acid of the arterial blood and that of the internal jugular vein They found that the average oxygen utilization for the pellagrin free of any evidence of clinical thiamine deficiency was 6 16 volumes per cent The average for those pellagrins with clinical thiamine deficiency was 4 6 volumes per cent The average for the entire group was 5 8 volumes per cent The normal subjects had excellent health with no evidence of pellagra beriberi or any deficiency and they had a value of 7 4 volumes per cent It seemed that a diminution of brain metabolism would best explain these findings Correlated with this diminished oxygen uptake is the average glucose utilization of 6 mgm per 100 c c No difference in utilization of lactic acid was noted between arterial and venous blood going to and coming from the brain These observations afford a basis for the explanation of the mental changes

observed in patients subsisting on an unbalanced high carbohydrate diet

It is known that vitamin B_1 is essential for the normal functioning of the alimentary tract but as yet we do not understand the exact mechanism by which it functions in predisposing to gastrointestinal disturbances In experimental animals and in human beings anorexia which is an early symptom of a deficiency of thiamine disappears promptly following the administration of thiamine Both the thiamine deficient animal and man following the administration of thiamine will eat food which they previously have refused Controlled studies with thiamine have shown that the normal tone of the alimentary tract is altered in persons with thiamine deficiency It has been observed that persons with early thiamine deficiency usually have little appetite and often are constipated Gastrointestinal series frequently show 'puddling' of the *barium in the small intestine Some of these persons improve impressively* following the administration of vitamin B_1 It is certain however that neither lack of appetite nor constipation are in any way specific manifestations of vitamin B_1 deficiency in human beings The breakdown in metabolism is primary and has a widespread effect on all the cells and the effects are not equally distributed in the body Eventually this failure to metabolize nutrients by the tissue cells halts many processes and we then find loss of appetite while as Peters graphically states there is internal hunger in the tissues

Vitamin B_1 is an essential factor for the normal growth of the young and for the maintenance of normal health for the adult It is particularly important however for the physician to realize that several factors operate concomitantly and that thiamine alone is not adequate to insure proper growth Vitamin B_1 deficiency often is associated with loss of libido in human beings and experimental animals There is a great need for vitamin B_1 during pregnancy and lactation The vomiting of pregnancy is common and this in itself may be associated with a deficiency of vitamin B_1 or it may lead to further vitamin B_1 deficiency Mothers who have vitamin B_1 deficiency predispose their nursing infants to thiamine deficiency

Pathological Physiology

Vitamin B_1 deficiency affects the cardiovascular system and the most common cause of sudden death from thiamine deficiency is acute cardiac failure The heart is dilated and enlarged in the classical case

It is of great interest that experimental deficiencies rarely result in serous *effusions and cardiac enlargement whereas in human beings they*

are not uncommon in the acute case of beriberi There is little doubt that cases of beriberi disease and cases of serous effusion have developed on a diet low in thiamine and that the administration of thiamine will relieve the symptoms Still, investigators have been unable to place this on an experimental basis whereby the experimental subject eats a vitamin B_1 deficiency diet and an inevitable sequence of cardiovascular disturbances occurs

The lesions of experimental vitamin B_1 deficiency appear identical with those occurring in vitamin B_1 deficiency in man and the majority of investigators regard experimental vitamin B_1 deficiency in animals as a disease analogous to this deficiency in man Degeneration of the nervous system occurs in most, if not all species with prolonged thiamine deficiency Experimental polyneuritis in fowls is very similar to dry beriberi in man most of the degeneration occurring in the peripheral nerves The sciatic nerves are especially involved Vedder and Clark[19] have shown that in both man and animals there is evidence of involvement of every fiber although the extent of degeneration is tremendously variable in the fibers of the same nerves The myelin degeneration may affect the peripheral nerves the ventral and dorsal nerve roots and the tracts of the spinal cord the medulla pons midbrain and the internal capsule

SYMPTOMATOLOGY

Various clinical forms of vitamin B_1 deficiency are described Each case, however presents great individual variations In the adult the onset usually is insidious The symptoms are characterized by cardiovascular disturbances neuritis and edema and these forms sometimes are termed "cardiac," "neuritic" or "wet" according to the prevailing symptoms

The clinical picture is one of symmetrical peripheral neuritis which is the most common finding and is associated with weakness, cramps in the legs and paresthesias and burning sensations over the soles dorsum of the foot and ankle The Achilles and patellar reflexes in the typical case are hyperactive early in the disease and later are absent The weakness spreads up the legs and the affected muscles become tender and numb Atrophy of the muscles and skin follows (Fig 3-) The upper extremities frequently become involved in the very severe cases the hands and arms being affected first Burning numbness and weakness may be followed by wrist drop The muscles of the trunk and diaphragm may become involved When edema is present it begins in the feet and legs

and ascends up the body and may mask the muscle wasting Anorexia diarrhea and vomiting may be associated with it Aphonia sometimes is seen in the adult and in infantile vitamin B_1 deficiency it is a common finding

Although severe mental symptoms usually do not develop memory difficulties and anxiety states are common and frequently are distressing



Fig 3 Bilateral marked atrophy of muscles of leg and feet foot drop is evident Case of vitamin B_1 deficiency

to the patient and his relatives Investigators[173] have learned that there is an amazing uniformity of the mental symptoms which have little connection with the personality The symptoms may be grouped as follows

A The Elementary Syndrome
  1 Psycho-sensory disturbances
  2 Psycho motor disturbances
  3 Emotional disturbances
B General Symptoms of the Central Nervous System
  1 Weakness and increased fatigability
  Sleeplessness
  3 Headache

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Diagnosis

Until a simple specific laboratory test becomes available a tentative diagnosis must depend upon the interpretation of a reliable medical and dietary history and a careful physical examination It is helpful to the *physician to bear in mind that vitamin B_1 deficiency occurs chiefly* among the following groups

1 The indigent and persons who have erroneous dietary habits and idiosyncrasies Such persons often subsist on a diet relatively abundant in overmilled rice wheat or corn Their diets rarely contain lean meat eggs milk fish fresh fruits or vegetables in sufficient amounts
2 Persons who have any organic disease that may interfere with the ingestion or absorption of an adequate diet the deficiency or metabolic diseases such as pellagra pernicious anemia sprue alcoholic neuritis Korsakoff s psychosis diabetes and myxedema Vitamin B_1 deficiency frequently is found in association with pregnancy and lactation hunger edema chronic colitis and cachexia from any cause Thiamine deficiency also is found frequently in association with diarrhea from any cause There is great danger of the physician s not recognizing isolated cases as true thiamine deficiency
3 Persons in whom the vitamin B_1 *requirement* is distinctly above the average because of growth pregnancy and lactation hard physical exertion hyperthyroidism and fevers

A diagnosis of uncomplicated thiamine deficiency can be made by excluding all other causes of peripheral neuritis organic heart disease edema and psycho-neurosis The mild case is much more common than acute case but it may be recognized only with difficulty Keeping in mind the following points noted by Vedder[108] is helpful in making an early diagnosis of the disease

1 *Slight pressure over the muscles of the calf causes pain*
Patients with beriberi often have areas of anesthesia over the anterior surface of the tibia
3 Any modification of the patellar reflexes is suspicious
4 If a patient with beriberi squats upon his heels after the Oriental manner of sitting he may experience pain and inability to rise without using his hands

In making a diagnosis of cardiovascular disturbances due to thiamine deficiency the big problem is to rule out heart disease of another etiol

The first group of symptoms resembles those which may be found in diseases of the basal ganglia and thalamus, while the second group represents general symptoms which usually accompany any disturbance of the central nervous system The complaints and responses to therapy are practically identical, whether the personality is simple or complicated or whether the patient is illiterate or educated Often there is a "break down of personality" during the early stages of developing deficiency

Detailed studies[191] of the emotional disturbances in persons with vitamin B_1 deficiency confirmed the findings that, in addition to the disturbed emotional reactions there was some impairment of the intellectual and cognitive functions Patients "jumped at the slightest sound" or "cried over the least little thing" No alteration in the electroencephalograms has been demonstrated despite the fact that within a short time after the injection of thiamine the symptoms subsided Injections of saline given in a similar manner did not produce any relief These emotional symptoms may occur in patients without deficiency disease, however and the authors recommend thiamine therapy only when such symptoms are associated with a deficiency state

Cardiovascular symptoms frequently are associated with fulminating acute types of thiamine deficiency known as "acute pernicious beriberi heart" If associated with edema it is called "wet" beriberi Many patients die suddenly from "beriberi heart" The original cases described by Wenckenbach and other clinicians in the Orient are characterized chiefly by right-sided failure Weiss and Wilkins[195] and the clinicians at the University of Cincinnati have examined a considerable number of patients with beriberi heart disease and the majority did not have right sided failure

Infantile vitamin B_1 deficiency usually occurs among infants in the first three months of life, and the onset is rapid The very early symptoms usually are vomiting and a distaste for food Attacks of pain frequently occur and result in the body's being held rigid although true convulsions do not appear The baby frets is constipated and often has edema considerable enlargement of the heart and cyanosis The blood pressure is low, the liver enlarged and the pulse rapid and irregular This form of the disease occurs chiefly in breast-fed infants whose mothers have a highly deficient diet Unless they are treated promptly, death occurs within a day or so

Prevention and Treatment

The Council on Foods and Nutrition of the National Research Council has made recommendations in regard to man's requirements for the various dietary factors necessary for normal physiological function In the chapter on riboflavin the table of the allowances for the various vitamins including vitamin B_1 is shown Beriberi and subclinical thiamine deficiency can be decreased greatly by the application of the following principles which will go far toward supplying these recommended allowances

1 Fresh foods such as potatoes native vegetables pork liver, eggs milk fruits beans and whole grain cereals should be included in the diet whenever possible
2 Since vitamin B_1 is water-soluble a large amount of it is lost when water in which foods are cooked is thrown away It is recommended that the water in which foods are cooked be used for broths and gravies Whole grain barley or other grains which are rich in thiamine, may be added to broths to afford additional protection
3 The use of undermilled or enriched flour cereals and cereal products is the greatest single improvement that can be made in the diet of the average person in respect to his thiamine intake and their use should be universal This is true particularly in low cost diets in which a preponderance of cereal foods is included necessarily because of their relatively low cost
4 Persons chronically addicted to alcohol and persons with sprue pellagra pernicious anemia colitis diabetes mellitus tuberculosis senility malignancy cirrhosis and many other diseases are prone to develop thiamine deficiency The incidence is high in persons with chronic debilitating diseases and increased metabolism Accordingly particular attention should be directed toward making the diet of such persons adequate
5 The diets of pregnant and lactating women should be especially rich in vitamin B_1 Whenever there is any doubt as to the adequacy or utilization of food either in the mother or in the child supplements should be given The supplements should be continued until the proper diet is assured The nursing mother should receive at least 5 mgm of thiamine or its equivalent daily the infant should receive 0 5 mgm or its equivalent daily

ogy The studies at the University of Cincinnati should be very helpful in this respect Blankenhorn, Vilter, Scheinker and Austin[19] have pointed out that the clinical picture of the failing heart with exceedingly rapid circulation is not likely to be overlooked, and such cases are more readily remembered than the less dramatic cases The first thought of thiamine deficiency in this type of heart disease is when the physician realizes that the etiological nature of the heart condition is obscure The elimination of coronary arteriosclerosis as a cause is difficult If the patient has no angina or precordial oppression no fever, no leukocytosis one is a little less likely to think of coronary disease or Fiedler's isolated myocarditis Since Williams, Mason and Smith[108] and Williams, Mason Power and Wilder[109], after inducing thiamine deficiency in man suggest that three months is about the development time of thiamine deficiency *Blankenhorn and his associates arbitrarily selected that point to aid in the evaluation of the clinical problem* Williams Mason and Smith observed electrocardiographic changes which they induced in subjects on thiamine deficient diets and abolished by thiamine administration Physicians in the field of nutrition, however, find that the electrocardiographic findings are non-specific, although they may aid in the final diagnosis

Heart disease caused by thiamine deficiency is uncommon in America but it does occur and it is curable The first suggestion that the heart disease may be the result of a deficiency of thiamine may come from one of a number of sources and the value of correlating the information obtained by the physician, the roentgenologist and the nutritionist cannot be overstressed The vivid description by Wenckebach[110] of the acute pernicious type of heart failure which is a valuable aid in making a diagnosis may be summarized as follows

1 Enlargement of the heart by percussion, auscultation and x ray examination
2 The presence of murmurs chiefly systolic but also presystolic with a resonant first sound The murmurs are increased disproportionately by exercise
3 Visible and palpable throbbing pulsations over the heart best felt just to the left of the sternum
4 Bounding pulse and thrill over the great arteries
5 Over-distended neck and arm veins and without exception a painful swollen liver In the most severe cases liver pulsation

A patient with the more common type of heart failure due to vitamin B_1 deficiency resembles any other case with degenerative heart disease Usually however, it is associated with edema and serous effusions

parenterally than when it is given by mouth When injections cannot be given conveniently or when the infant is convalescent 10 mgm of crystalline vitamine B1 may be given orally every day Obviously satisfactory treatment of the mother will aid greatly in the treatment of the nursing child

Toxicity

The practicing physician should have in mind that there is a great difference between the therapeutic and the toxic dose of thiamine The authors who have been studying this vitamin for ten years have seen no evidence of cumulative toxicity in human beings We have given as much as 500 mgm daily to patients for a period of sixty days without any evidence of toxic effects Since the therapeutic dose in man is only a few milligrams a day we consider it a remarkably safe therapeutic agent We have reported that large amounts of synthetic crystalline material when injected intravenously frequently cause the patient to volunteer that he experiences a yeast like taste There is no doubt that some persons have an idiosyncrasy to this substance just as they may have other drug idiosyncrasies and patients may become hypersensitive in the course of treatment

6 In persons with fever, severe gastrointestinal symptoms, hyperthyroidism and other conditions the requirement for vitamin B_1 may be distinctly above the average It is essential for the physician to prescribe amounts above the average for such persons For such a maintenance dose the authors suggest 5 mgm to 10 mgm of synthetic thiamine daily or its equivalent except when the patient is unable to absorb from the gastrointestinal tract In such instances it is essential that vitamin B_1 be given parenterally in order to protect the person from a deficiency of this vitamin

In the treatment of thiamine deficiency the problem is simply one of administering adequate amounts of thiamine in the way in which it can be utilized In the adult and infant the physician should direct therapy along three lines

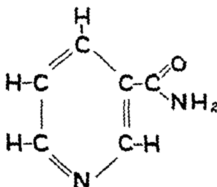
1 There should be elimination of conditions causing excessive requirement for vitamin B_1 whenever possible
2 Synthetic thiamine or its equivalent should be administered in amounts sufficient to correct the deficiency
3 There should be symptomatic treatment and treatment for coexisting diseases

The essence of successful treatment lies in the administration of adequate amounts of foods rich in thiamine, supplemented with large amounts of a specific therapeutic agent The diet should contain liberal amounts of liver, pork lean meats, eggs whole grain or enriched bread and cereals, beans peas and native vegetables and fruits It should be supplemented with the following curative therapeutic substances, 6 ounces of dried brewers' yeast daily, 6 ounces of wheat germ daily or 10 mgm of synthetic thiamine twice daily In cases of severe thiamine deficiency even larger doses of synthetic thiamine may be indicated In such cases it seems wise to administer 10 to 20 mgm twice daily until the signs of thiamine deficiency have disappeared In cases of mild deficiency doses of 10 mgm daily are adequate There is no question but that the oral administration of thiamine in adequate doses is efficacious in the average case Parenteral administration of 25 mgm twice daily is recommended however, when the deficiency is associated with severe cardiac failure, severe peripheral neuritis or severe gastrointestinal disturbances or when the patient is refractory to oral therapy

Infantile thiamine deficiency is treated most satisfactorily by giving intramuscularly or intravenously 5 to 10 mgm of thiamine in sterile physiological solution of sodium chloride twice daily As in the adult the action is more prompt and more efficacious when it is administered

which melts at 230 to 232° C It is moderately soluble in hot water but only slightly soluble in cold water The sodium salt and the amide are more soluble For parenteral administration the amide is preferable because it does not cause the flushing produced by nicotinic acid

Nicotinic acid is very stable and is not oxidized or destroyed by ordinary cooking processes or by exposure to light



Nicotinic Acid Amide
3 pyridine carboxylic acid amide

Fig 34 Structural formula of nicotinic acid amide

It is widely distributed in foodstuffs but even the richest sources such as liver eggs salmon and whole cereals contain relatively little of this substance

Relationship between Co enzymes I and II and Nicotinic Acid Amide Deficiency

The spectacular clinical improvement which follows the administration of nicotinic acid or nicotinic acid amide to pellagrins led to increased interest in the respiratory co enzymes I and II cozymase and coferment respectively which are known to contain nicotinic acid amide By definition these co enzymes are relatively heat stable dialysable organic catalysts which retain activity even when separated from the living cell They are necessary for the function of specific protein

NICOTINIC ACID AMIDE

History

Nicotinic acid was first prepared from nicotine by Huber in 1867[91], but its significance in nutrition was not discovered for many years. Between 1912 and 1916 it was isolated from rice polishings by Susuke, Shimamuri and Odake[92], Funk[93] and Williams[94,95] and in 1936 Vickery[96] found it in yeast. The amide of nicotinic acid was shown to be the active group of the coenzyme now known as coenzyme II by Warburg and Christian[97] in 1935, and at the same time Kuhn and Vetter[98] isolated it from the red blood cells of the horse and from mammalian heart muscle. As a result of this work the interest of many investigators was directed toward discovering the role of nicotinic acid in nutrition. In 1937 Elvehjem, Madden, Strong and Wooley[99] isolated it from liver and showed that it was curative in canine black tongue. Independently and almost simultaneously excellent results in treating human pellagra were reported by several investigators[10, 11, 12, 13].

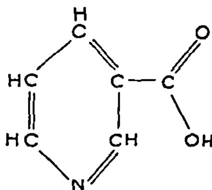


Fig 33 Structural formula of nicotinic acid (3 pyridine carbolic acid)

Chemistry and Physiology

There are several ways of preparing nicotinic acid, one of which is the strong acid oxidation of nicotine. It was from this method of preparation that nicotinic acid received its name. The formula for nicotinic acid is shown in Fig 33, that for its amide in Fig 34. Its properties, however, differ widely from the parent compound. Nicotinic acid, the beta carboxylic acid of pyridine, is a white crystalline compound (Fig 35)

studies a method specific for co enzyme I was used and it had no bearing on the co-enzyme II content of the tissues The precise significance of this lowering in the co-enzyme I content of the pellagrin s muscles can not be fully stated Unpublished observations by Lu and Spies[18] indicate that the changes in the oxidative metabolism of the striated muscle taken from the pellagrin are less than those found in normal controls These investigators observed that following therapy normal values in the muscles of pellagrins soon were restored The anti pellagric value of a substance however is not necessarily associated with its ability to affect the co-enzyme I content of the blood and other tissues For example nicotinic acid has a profound effect upon the co-enzyme I content of human blood both in vivo and in vitro while coramine, the diethylamide of nicotinic acid which is also anti pellagric does not produce a significant increase in the co enzyme I content of erythrocytes and muscles

The fact that the very ill pellagrin may have only 60 per cent of the normal concentration of co-enzyme I in his muscles offers a marvelous explanation of the long lingering weakness which characterizes the period of development of dietary deficiency disease Spies von Euler Vilter Bein and Schlenk in unpublished observations have shown that the intravenous injection of from 10 to 50 mgm of co-enzyme I of the highest activity is followed by dramatic clinical improvement in the acute manifestations of pellagra yet this amount when distributed throughout the body is not detectable by their highly sensitive laboratory methods

Absorption, Distribution Excretion and Effects

Unpublished observations by Bean Dexter and Spies showed that nicotinic acid is absorbed from the stomach and from the small and large bowel Absorption is more rapid from an empty stomach than it is after meals If the absorption is sufficiently rapid the concentration of nicotinic acid is increased in the blood and the skin temperature of the upper part of the body is elevated Over 80 per cent of the persons to whom 100 to 300 mgm of nicotinic acid is administered orally feel temporary prickly or burning sensations of the skin A few persons complain of nausea and cramping pains in the stomach These symptoms are transitory and are not associated with changes in general body temperature pulse respiration or blood pressure All persons to whom 20 mgm of nicotinic acid is administered rapidly by the intravenous route have transitory vasodilation It should be remembered however

enzymes Each is produced by living cells from a combination of nicotinic acid amide, ribose, adenylic acid and phosphoric acid The present knowledge of the chemical constitution of co enzymes I and II indicates that they are similar in that both are pyridine nucleotides, differing only in their content of phosphoric acid The authors of this chapter consider that the formation of enzymes governing respiration and growth of cells involves the synthesis of complex substances from simple compounds

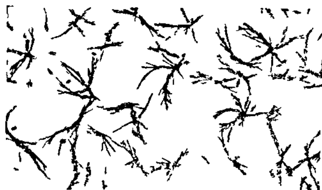


Fig 35 Crystalline nicotinic acid (courtesy of Merck and Co)

The methods for studying the enzymes are tedious and are not recommended for the practicing physician Nevertheless they offer important information concerning certain aspects of the pathogenesis of pellagra and other diseases Vilter Vilter and Spies[11] found that the concentration of co-enzymes I and II in the whole blood of persons with deficiency diseases is slightly lower than in normal persons on optimal diets Low values for the co-enzyme concentration of whole blood may be observed also in some persons with diabetes mellitus, roentgen sickness leukemia and pneumococcal pneumonia Infections, fever and excessive physical exercise tend to lower the concentration in the blood whereas rest in bed and an increased intake of nicotinic acid or related pyridine compounds tend to increase the concentration

Axelrod Spies and Elvehjem[1] studied a large series of pellagrins admitted to the Nutrition Clinic at the Hillman Hospital in Birmingham Alabama Using a yeast growth method which is specific for co-enzyme I, they found that there was only a slight lowering of this substance in the erythrocytes There was a great decrease in the co enzyme content of the striated muscle and it continued to decrease as the pellagra became more severe, whereas it increased following the administration of nicotinic acid or nicotinic acid amide It should be emphasized that in these

metabolic derivative chiefly excreted The co-enzymes I and II increase in the blood and urine after nicotinic acid is administered

Nicotinic acid compounds have been found in nearly all animal tissue In general the concentration is highest in tissues in which the metabolism is high In human beings with severe nicotinic acid deficiency the concentration of the nicotinic-acid amide-containing substance co enzyme I is decreased as much as 60 per cent in striated muscle and *may be slightly decreased in the erythrocytes.* Likewise in this deficiency the content of the nicotinic acid derivatives is below normal in whole blood and urine When such patients are treated with nicotinic acid the content of the compounds in the muscle blood and urine containing nicotinic acid amide increases

A knowledge of the level of nicotinic acid in the body tissues and excretions of pellagrins sometimes contributes valuable information concerning the degree of nicotinic acid deficiency It also is useful in following the rate of recovery after nicotinic acid therapy has been initiated Several methods both chemical and microbiological for the determination of nicotinic acid in micro quantities have been introduced In studying biologically derived specimens we use the microbiological technics because they possess extreme sensitivity permitting the determination of nicotinic acid in amounts as small as a few hundredths of a microgram and may be used in analyzing for nicotinic acid in the presence of large amounts of foreign material even if this be pigmented or in a solid state The microbiological method of Snell and Wright has been used successfully in determining minute quantities of nicotinic acid in blood urine feces saliva fresh tissues and foods Using this method Gross Swain and Spies[17] have found that the average person with pellagra retains more of a 100 mgm test dose of nicotinic acid than does the normal person of similar size

Pigment Metabolism

In 1913 Myers and Fine observed that indicanuria was pronounced in pellagrins in the presence of low hydrochloric acid in the gastric contents Three years later Hunter showed that the previous diet was important in the determination of the fate of additional ingested tryptophane and reported the finding of urorosein in the urine of pellagrins Studies by the authors show that many pellagrins excrete indole indican urorosein and various other related compounds in the urine A number of investigators have found porphyrin in the urine of pellagrins At one

that nicotinic acid amide is the more physiological form of the compound, and it does not produce these vasodilating reactions. There is some tendency for the blood vessels of the lower extremities to constrict following the administration of nicotinic acid, and the amounts and methods of administration have a profound effect on the skin temperature rise as is shown in Fig. 36.

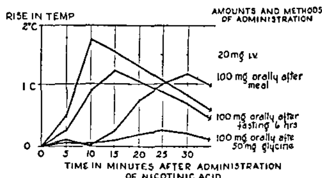


Fig. 36. Skin temperature rise after nicotinic acid (from Duncan Graham. Disease of Metabolism. W. B. Saunders Co. Phila. 194)

Nicotinic acid amide and co-enzymes I and II are present in the blood and are excreted in the urine. These substances are so essential that the body does not allow the blood levels to be lowered greatly. The amount excreted in the urine is dependent upon many factors including the richness of the diet and the concentration in the body tissues. When they are administered in pure form the amount excreted depends on the size of the dose and the mode of administration. Excretion is more rapid when the material is administered parenterally than when it is given orally. When large doses of nicotinamide are injected into human beings, the material cannot be accounted for either unchanged or as known derivatives in the urine. Even after repeated doses large amounts do not appear in the urine and therefore, must be metabolized in ways at present unknown. The metabolic derivative of nicotinamide is N-methyl nicotinamide. Even after repeated injections of this substance it does not, for the most part, appear in the urine. It should be emphasized that for a long time it was taken for granted that human beings excreted trigonelline, the methyl betaine of nicotinic acid as do dogs. It is known now that N methyl nicotinamide is the

clinically affected and unaffected areas in pellagrins was hyperkeratotic. Parakeratosis was found also in the actual lesions. No satisfactory explanation of the atrophy which is present both in healing pellagrous lesions and in the unaffected skin can be given. That atrophy occurs normally with aging of the skin and that it may result from either external or internal pressure has long been known, but the exact mechanism involved in the process remains unexplained, and the present study affords no new information concerning it. Both the affected and unaffected skin showed edema of the corium and a moderate infiltration of lymphocytes. Since the skin lesions tend to disappear following treatment with nicotinic acid, they are to a considerable extent reversible so it seems that they represent a specific response on the part of the skin to a deficiency of nicotinic acid and substances that act similarly. The microscopic picture of the intestinal lesions varies from atrophy to acute inflammation characterized by fibrin formation and collections of inflammatory cells. When changes in the nervous system are demonstrable they are characterized by irregular areas of degeneration, often involving the posterior and lateral columns of the spinal cord, the posterior spinal ganglia and the Betz and Purkinje cells.

SYMPTOMATOLOGY

As is shown in Fig. 37, there is a lag period between the onset of symptoms and the time the patient seeks medical aid. The time between the very first day of dietary deficiency and the appearance of lesions might well be termed the deficiency development time. This period of time may be of long duration with insidiously advancing symptoms trivial in nature but gaining importance by their persistency rather than by their severity. Before diagnostic lesions of the mucous membranes or skin appear, there is loss of appetite which is, at least in part, responsible for weight loss. Ill defined disturbances of the alimentary tract including indigestion and changes in bowel function occur. General muscular weakness, lassitude, irritability, depression, memory loss, headache and insomnia frequently develop without apparent reason. Abdominal pain, burning sensations in various parts of the body, vertigo, numbness, nervousness, palpitation, distractability, flights of ideas, apprehension, morbid fears, mental confusion and forgetfulness frequently occur. There may be intermittent diarrhea and constipation. There is much that obviously is abnormal at this stage but nothing that is pathog

time it was thought that the excretion of porphyrin might be useful as a diagnostic test It now appears that porphyrinuria is a result of liver damage or at least a disturbance of liver function Naturally the alcoholic pellagrin is more prone to have liver disease than the endemic pellagrin Urorosein and indican frequently are excreted in large amounts in early or subclinical pellagra, so that their detection may serve as a valuable warning signal of malnutrition The test using colorimetric methods is a simple but non-specific one The procedure is as follows

A measured amount of urine (3 to 10 c c) is acidified with glacial acetic acid to a pH of about 4 0 and shaken with 5 to 20 c c of ether until no more red pigments can be extracted The ether then is washed repeatedly with water A complete separation of the two layers is allowed to take place To a measured fraction of the ether is added one fifth of that amount of 25 per cent hydrochloric acid On shaking the pigments contained in the ether fraction are transferred completely to the hydrochloric acid which becomes stained purple or pink the intensity of the color depending on the pigment concentration The colorimetric estimation is made either in a colorimeter of Dubosq type against a standard solution of porphyrin or by comparison with porphyrin solutions of known concentration The time necessary for the complete transfer of the porphyrins from the urine into the ether and from the ether into hydrochloric acid differs in various specimens being determined by the nature of the substance present In most specimens the process is completed in a half an hour, but as a check the colorimetric estimations may be repeated after three hours and after twenty four hours

Severe cases may have a negative test

Pathological Physiology

The most common gross pathological findings of nicotinic acid deficiency are generalized emaciation of the body and atrophy of various organs In some cases the walls of the gastrointestinal tract may show swelling, reddening and ulceration of any portion, while in other cases the walls may be thin and atrophic The liver occasionally contains abnormal amounts of fat Moore Spies and Cooper[218] made a histologic study of the active lesions and also of clinically unaffected areas of the skin in the same patient

The microscopic picture of the lesions of pellagra is similar to that found in chronic inflammatory diseases of the skin The skin from both

appetites and eat irregularly As a rule they prefer carbohydrate foods and often refuse all others Usually they develop poor food habits early in life and the parents seldom make any attempt to change them even if a good diet becomes available The parents frequently complain that the children are irritable easily frightened apprehensive fretful and cry a great deal, that they are too tired to play but too nervous to rest that they sleep poorly and frequently awaken crying Few of them gain weight normally, and the few, who were robust prior to their illness usually have lost weight rapidly In these children soreness of the lips and tongue and burning of the stomach are common complaints as are pains in the abdomen cramping of the legs and cramping and burning of the feet Usually they are constipated but have occasional bouts of diarrhea during the spring and summer These symptoms wax and wane and become more severe with each recurrence As the children grow older the subnormality in height and weight usually becomes more apparent as does an increasing inability to concentrate or to make normal progress in school From the physical examination it is obvious that these children are in ill health They appear undernourished and underdeveloped for their age Usually their skin is dry and atrophic making them appear much older than they are The typical dermal and alimentary tract lesions described in adult pellagra may or may not develop A more complete discusion of pellagra as a disease will be found in Chapter XIII Vol IV of Oxford Medicine

Diagnosis

The clinical diagnosis of pellagra in adults or children depends upon identifying typical dermal lesions or characteristic mucous membrane lesions or both

Characteristic skin lesions may appear on any part of the body They are observed most frequently over sites of irritation such as the dorsum of the hands wrists elbows face neck knees feet under the breasts and in the perineal region In most instances the area of dermatitis is separated sharply from the normal skin The lesions are never static they either advance or regress The dermatitis begins as an erythema resembling sunburn As the disease progresses the area becomes reddish brown roughened scaly and keratotic vesicles and bullae may form Desquamation usually begins at the center of the lesion and the underlying skin appears red and thickened The intensity of the pigmentation

nomonic Since the entire syndrome often appears without objective cause a diagnosis of neurasthenia anxiety state malingering or neurosis may be entertained by the physician These symptoms are not invari

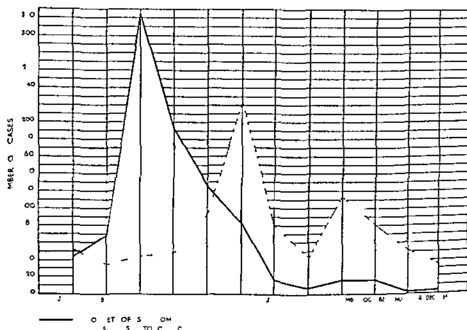


Fig. 37 Lag period between onset of symptoms and first visit to clinic

ably present, they *do not appear in any regular order* and they are not uniformly severe in every case The individual case, however, usually repeats the same order of development of symptoms with each recurrence

Although the identity of pellagra in children and adults is established the clinical manifestations often are different and for purposes of clarity it is advisable to consider them separately It should be borne in mind however, that from an etiological and pathological point of view such a distinction is artificial

Endemic pellagra in infants and children has been reported by Spies Walker and Woods [19] These investigators find that a careful dietary history of the mother usually reveals that her diet has been inadequate during pregnancy and lactation Frequently her milk supply is scanty and the infant is weaned soon after birth and given food inadequate for proper nutrition or the inadequate breast milk feedings are supplemented with such foods From an early age most of the children have poor

phasized for many years The patient may present a train of symptoms characteristic of neurasthenia anxiety state or other neuroses In later stages there is loss of memory excitement mania delirium hallucinations and dementia Even in the absence of diagnostic lesions of pellagra the patient may have central nervous system involvement

A series of severe cases of pellagra with atypical lesions has been described by Spies Cogswell and Vilter[27] This type of case is difficult to diagnose and is likely to be fatal if proper therapy is not applied promptly

A history of prolonged subsistence on a deficient diet plus the presence of pellagra in other members of the family should lead the physician to suspect pellagra even in the absence of typical pellagrous lesions When there is any doubt the controlled therapeutic test should be given since it is known that if early pellagra is present rapid improvement will follow specific therapy

Prevention and Treatment

Like most nutritional deficiency states nicotinic acid deficiency is particularly prevalent among the following groups and it is to these groups that special attention toward prevention should be directed

1 The poor and ignorant who subsist on an unbalanced diet usually rich in cereals and low in meat milk and eggs Casal who first described pellagra pointed out that mal de la rosa occurred among people who ate corn for a staple cereal Endemic pellagra has occurred almost exclusively among people who ingest corn or corn products The hypothesis that corn plays a role in the etiology of the disease has commanded continued attention After finding that nicotinic acid was a useful therapeutic agent investigators have been much interested in possible antagonism between it and corn Evidence of this antagonism has been extended by the observations of Krehl Sarma Teply and Elvehjem[26] who showed that cornmeal or corn grits added to a low protein diet greatly reduced the growth of young rats and that addition of 1 mgm of nicotinic acid per 100 grams of diet restored growth to the level observed when the diet contained no corn products These investigators next learned that tryptophane could overcome the growth inhibitors present in the corn products It is of considerable dietary interest that polished rice contains less nicotinic acid than corn but more tryptophane From a clinical point of view it is of great interest that pellagra occurs

and the thickening of the skin tend to increase with each recurrence of the disease After repeated recurrences the skin may become either permanently pigmented thick and roughened or thin and atrophic In the past a diagnosis of pellagra was not ventured unless well established bilateral lesions were evident Such lesions are much more common than unilateral lesions Nevertheless Bean, Spies and Vilter[illegible] found 3[illegible] patients with well advanced unilateral pellagrous dermatitis in a series of 889 cases These investigators emphasize that in their experience the cutaneous lesions in different parts of the body often are in different phases simultaneously One lesion may be at the stage of early erythema another in the stage of desquamation, and still another in the stage of pigmentation Sunlight as the exciting agent of pellagrous dermatitis has been discussed for years by many investigators Some of the series of opinions have been discussed by Smith and Ruffin[1], Spies[illegible] and Stannus[3] Suffice it to say that lesions not exposed to the sun occur but it is generally agreed that exposure to sunlight is more detrimental to pellagrins than it is to normal persons

Glossitis and stomatitis are early and common symptoms of pellagra and Spies[illegible] has demonstrated that pellagrous glossitis is a much more sensitive gage than dermatitis in the evaluation of the severity of the disease In the early stage of the disease only the tip or the lateral margins of the tongue are swollen and reddened In the absence of treatment the swelling increases redness becomes more intense and deeply penetrating ulcers may appear along the sides and tip but rarely on top The entire surface may be covered with a thick gray membrane filled with debris and Vincent s organisms The tongue may be hypersensitive, although it usually is hypoesthetic The buccal mucous membranes, the mucocutaneous surface of the lips, the gums and the palate likewise may be affected A burning sensation of the tongue and of the mucous membranes of the pharynx esophagus and stomach is not uncommon and usually is aggravated by hot or acid foods Ptyalism and nausea may occur early but, as a rule they are advanced symptoms of the disease Achlorhydria is present in about 50 per cent of persons with pellagra even after histamine stimulation rennin and pepsinogen likewise are absent In the majority of mild cases the bowels act normally or are constipated Severe persistent diarrhea with frequent watery stools tends to occur only in the more acute cases Abdominal discomfort pain and distention may be present at any time during the course of the disease and usually are more severe after a large meal

Mental symptoms as a part of the pellagra syndrome have been em

Vegetables and Fruits
- Six to seven servings daily
- One serving daily of tomatoes or citrus fruits
- Two and one half to three servings daily of vegetables at least half of which are leafy green or yellow kinds
- Nine to ten servings a week of fruit (once a day sometimes twice)

Eggs
- Four to six a week also some in cooking

Meat fish or poultry
- Once a day, sometimes twice

Butter
- At every meal

Bread cereals and desserts
- As needed to meet caloric requirements or as desired so long as they do not displace the protective foods

In areas in which pellagra is endemic the authors find that the disease usually occurs in persons whose diets have been deficient in animal proteins and relatively high in cereal foods and fats

We have found that it is more practical to add to the existing dietary daily one half pound of lean meat two eggs from one pint to one quart of milk and liberal amounts of vegetables than it is to try to change completely long established dietary habits When such additions are not available or practical we have found that daily supplements of concentrates such as dried brewers yeast or liver extract are excellent preventive agents In such cases we recommend two ounces of dried brewers yeast or liver extract Persons who do not absorb or utilize the nutrients properly or whose requirement for them is increased are special medical problems The authors have found that to maintain good health in some cases it is sufficient to give additional amounts of the foods mentioned above In others, however the administration of niacinamide is necessary In these cases we usually begin with an oral dose of from [illegible]0 to 50 mgm daily In those rare cases in which absorption is so meager that this oral dose is not adequate [illegible]0 mgm daily is given by intravenous injection In administering niacinamide or any single synthetic substance it is important for the physician always to keep in mind that the factors which predispose to or precipitate the development of one deficiency lead to the development of others It likewise is important for him to realize that the administration of niacinamide alone may result in improved health but it will not restore it completely Thus for every

in persons who have never eaten maize (corn) but most of the endemic pellagrins of the world are heavy corn eaters Pellagrins who normally have a low level of vitamins in their tissues, would be most susceptible to any deleterious action of corn Pellagrous lesions heal spectacularly while the patient is restricted to a diet of corn products, if adequate amounts of nicotinic acid are administered

2 Persons who because of organic diseases have difficulty in ingesting assimilating or utilizing food In this group are included persons whose diseases predispose them to pellagra which usually is referred to as pellagra secondary to organic disease More males than females have pellagra secondary to cancer and ulcer of the stomach In pellagra following measles and whooping cough children naturally predominate Childbearing and its associated complications predispose women from 20 to 40 years of age to pellagra if their diets are of borderline adequacy, and the incidence is highest among women in this age group Bean, Spies and Blankenhorn have discussed the perilous burden which organic disease and surgical operations place on the undernourished

3 Persons who are chronically addicted to alcohol and who eat very little food frequently develop pellagra which often is referred to as alcoholic pellagra or pseudo pellagra

4 Food faddists and persons with capricious appetites, who tend to eat little food containing anti pellagric substances and persons who have subsisted on diets prescribed by physicians for certain diseases diets which fail to supply adequate amounts of the pellagra-preventive factor

5 Persons whose requirements for the anti-pellagric substances are increased Pregnancy lactation rapid growth hyperthyroidism, infections and increased physical exercise are all factors which increase the requirement

It is much better for a potential pellagrin to eat sufficient amounts of lean meat, eggs milk and vegetables and thus prevent the disease than it is for him to have to be treated for pellagra Satisfactory diets taking into consideration the daily allowances of nutrients recommended by the Council on Foods and Nutrition of the National Research Council have been planned at different levels of cost by Carpenter and Stiebling [9] and will serve as an excellent guide for the physician The liberal diet plan which they suggest provides the following variety in the course of the day or week

Milk

One quart daily for each child (to drink or in cooked food)

One pint daily for each adult (to drink or in cooked food)

4 P.M. Ice Cream—1 serving
5 P.M. Cereal Gruel—1 serving
6 P.M. Eggnog—1 glass
7 P.M. Cream Soup—1 serving
Ice Cream—1 serving
8 P.M. Eggnog—1 glass
9 P.M. Eggnog—1 glass

Note cup = standard 8 ounce measuring cup
glass = 8 ounce water glass

Approximate Food Value of Diet
Protein 145 gms.
Total Calories 4 134

4,000 CALORIE LIQUID DIET

Suggested Feedings Every Two Hours

7 A.M. Fruit Juice with egg—1 glass (see recipe)
Cereal Gruel—1 serving (see recipe)
9 A.M. Eggnogg—1 glass (see recipe)
Ice Cream—1 serving
11 A.M. Eggnogg—1 glass
Milk—1 glass
1 P.M. Cream Soup—1 serving (see recipe)
Eggnog—1 glass
Ice Cream—1 serving
3 P.M. Eggnog—1 glass
Milk—1 glass
5 P.M. Eggnog—1 glass
Ice Cream—1 serving
7 P.M. Cream Soup—1 serving
Ice Cream—1 serving
Eggnog—1 glass
9 P.M. Cereal Gruel—1 serving
Eggnog—1 glass
11 P.M. Eggnog—1 glass

Note cup = standard 8 ounce measuring cup
glass = 8 ounce water glass

Approximate Food Value of Diet
Protein 145 gms
Total Calories 4 134

pellagrin or every potential pellagrin the regular consumption of a liberal well balanced diet is of utmost importance

The dietary treatment of patients with pellagra, whether they are in bed at home or in the hospital or whether they remain ambulatory is based on the principles of good nutrition It must be remembered however that the tissue stores of niacinamide as well as of the other essential nutrients are likely to be severely depleted Accordingly the diet must supply much more than the allowances of nutrients recommended for normal persons We recommend that the diet supply from 3 000 to 4 000 calories *120 to 150 grams of protein* and liberal amounts of minerals and vitamins The type of food prescribed and the form in which it is given depend entirely upon the ability of the patient to ingest and retain food Frequently the patient s desire for food is absent, and he has to be persuaded to eat In the severely ill patient the mouth and tongue may be so sensitive that only soft or liquid foods can be tolerated and highly seasoned or acid foods must be avoided In some instances only a small amount of food can be taken at one time and it is necessary to give small feedings at frequent intervals As the patient improves semi solid and solid foods can be given In all cases with diarrhea solid foods should be added as soon as possible In the dietary treatment of pellagra and other nutritional deficiency diseases we have found the following diets* useful

4 000 Calorie Liquid Diet

Suggested Hourly Feedings

7 A M	Cereal Gruel—1 serving (see recipe)
	Milk—1 glass
8 A M	Eggnogg—1 glass (see recipe)
9 A M	Eggnogg—1 glass (see recipe)
10 A M	Ice Cream
	Fruit Juice with Egg (see recipe)
11 A M	Eggnogg—1 glass (see recipe)
12 Noon	Cream Soup—1 serving (see recipe)
	Milk—1 glass
1 P M	Eggnog—1 *glass*
2 P M	Ice Cream—1 serving
3 P M	Eggnog—1 glass

* These diets were planned by Miss Jean M Grant dietitian Nutrition *Clinic* Hillman Hospital Birmingham Alabama

4 000 CALORIE 'SOLID' DIET

Suggested Meals and Between Meal Feedings

Breakfast	Fruit Juice – 1 glass Cereal – large serving Eggs – 2 Bacon or Ham – if desired Toast – 2 slices Butter – pats Cream – ½ cup (for cereal and coffee) Milk – 1 glass Coffee – if desired
10 A M	Eggnog – 1 glass (see recipe)
Dinner	Lean Meat Chicken or Fish – 3 ounces Potato macaroni spaghetti noodles or dried beans or peas (1 serving) Vegetable – large serving (green or yellow vegetable – may be cooked or used as salad If cooked add 1 square of butter if used as salad, add 1 tablespoon mayonnaise) Bread – slices Butter – . pats Dessert – 1 serving Milk – 1 glass
2 P M	Eggnog – 1 glass
4 P M	Eggnog – 1 glass
Supper	Lean Meat Chicken or Fish – 3 ounces Potato macaroni spaghetti noodles or dried beans or peas (1 serving) Vegetable – large serving (green or yellow vegetable – may be cooked or used as salad If cooked add 1 square of butter if used as salad, add 1 tablespoon mayonnaise) Bread – slices Butter – pats Dessert – 1 serving Milk – 1 glass

4 000 Caloric "Soft-Solid" Diet

Suggested Meals

Breakfast, 8 A M	Fruit Juice—1 glass
	Cooked Cereal—1 serving (½ cup)
	Cream—¼ cup
	Sugar—2 teaspoons
	Soft Cooked Eggs—2
	Milk Toast—Toast 1 slice
	Milk ½ cup
	Butter, 1 square (2 teaspoons)
	Milk—1 glass
	Coffee—if desired
10 A M	Eggnogg—1 glass (see recipe)
	Ice Cream or puddings—1 serving
Lunch 12 Noon	Cream Soup—1 serving (see recipe)
	Soft Cooked Eggs
	Milk Toast—Bread 1 slice
	Milk, ½ cup
	Butter 2 teaspoons
	Mashed Potato or Boiled Rice — 1 serving (½ cup)
	Butter — 1 pat (2 teaspoons)
	Ice Cream or Pudding — 1 serving
	Milk — 1 glass
2 P M	Eggnog — 1 glass
4 P M	Eggnog — 1 glass
Supper, 6 P M	Cream Soup — 1 serving
	Cooked Cereal — ½ cup
	Cream — ¼ cup
	Sugar — 2 teaspoons
	Soft Cooked Eggs — 2
	Ice Cream or Pudding — 1 serving
	Milk — 1 glass
8 P M	Eggnog — 1 glass

Note cup = standard 8 ounce measuring cup
Glass = 8 ounce water glass

Approximate Food Value of Diet

Proteins	147 gms
Total Calories	4 153

it is administered by any other route We have observed one patient with long standing pellagra however who failed to respond to oral doses of niacinamide as high as 1 500 mgm daily but who improved rapidly following the intravenous administration of 50 mgm 6 times a day

Parenteral therapy is indicated when a high blood concentration is desired within a short period of time when gastrointestinal absorption is inadequate or when the patient is in stupor or coma In such cases 50 to 100 mgm doses are sufficient In order to keep the blood concentration at a high level it should be administered in small doses at frequent intervals The authors give 50 mgm doses 4 times daily and inject it slowly When parenteral administration of saline or glucose is indicated in the acutely ill patient the vitamin can be dissolved in a physiological solution of saline or 5 per cent glucose and administered by slow drip

Niacinamide can be given intramuscularly in the same dosage as that suggested for intravenous injection Intramuscular therapy is not recommended for persons with deficiency disease however because it is attended by some risk of abscess formation in devitalized tissues

A satisfactory daily dose for infants is from 50 to 100 mgm dissolved in the infant s total milk supply for the day For parenteral administration we suggest 15 mgm 3 times a day If the infant is breast fed the niacinamide can be given to the nursing mother[11] This increases the niacinamide content of the mother s milk sufficiently to relieve the infant s deficiency For children two or three times the dose recommended for infants is suggested and should depend upon the size of the child

Adequate doses of niacinamide or similar substances administered to a pellagrin will (a) cause fading of the fiery redness of the mucous membrane lesions and disappearance of the associated Vincent s organisms (b) cause disappearance of the acute mental symptoms of pellagra such as delirium hallucinations and mental confusion (c) relieve diarrhea vomiting and cramping which arise from alterations in alimentary function, (d) cause fading of the dermal erythema (e) increase the feeling of strength and well being (f) result in disappearance of certain ether soluble red pigments from the urine (g) increase the concentration of co-enzymes I and II in whole blood and urine and when therapy is prolonged increase the co-enzyme content of the muscle We wish to stress, however that in treating pellagra or any other nutritional deficiency disease, the patient as well as his disease must be treated

8 P M	Eggnog — 1 glass	
	Approximate food value of diet	
	Protein	148 Gm
	Total Calories	3,980

Recipes

Eggnog	6 eggs, 4 tablespoons sugar, 6 cups milk Beat eggs Add sugar Add milk Beat mixture well Chocolate syrup or vanilla may be added if desired *Makes 8 servings*
Cereal Gruel	½ cup of any kind of cooked cereal thinned to desired consistency with milk and served with ¼ cup of cream and with sugar, if desired
Cream Soup	¼ cup strained vegetable or canned tomato pea spinach or asparagus soup Add ½ cup cream
Fruit Juice with Egg	Beat 1 egg well Add 1 cup fruit juice Add sugar as desired

It should be pointed out, however that in certain diseases such as allergy, diabetes and gastric ulcer which necessitate restricting the kind or amount of food, these diets would not be suitable Such cases require individual diet therapy a detailed discussion of which is beyond the limits of this chapter

Important as food is in the treatment of nutritive failure, therapy should not be restricted to food alone Deprivation of nutrients usually has existed for years and the average patient cannot eat enough food to supply the amount of these nutrients necessary to restore his health quickly Accordingly supplements of the nutrients in which the diet is deficient are given Until synthetic vitamins became available dried brewers' yeast powder, wheat germ, liver concentrates and citrus fruit were given in treating deficiencies of the water-soluble vitamins As valuable as these substances were, and still are, there are times when niacinamide is life-saving

The amount of niacinamide or similar compounds necessary for a therapeutic response in pellagra varies tremendously from patient to patient so that no arbitrary dosage can be set In the average case we have found that 50 mgm administered orally 10 times a day is effective Oral administration of niacinamide is preferable to other methods because by this route it is absorbed more slowly, and an elevated blood concentration is maintained over a longer period of time than it is when

RIBOFLAVIN

History

The scientific world paid scant attention when Blythe[?] the English chemist reported the presence of a fluorescent yellow green substance in milk in 1867 Blythe himself was interested primarily in learning something about the composition of milk and little did he realize that the pigment which he described would later play a role in the science of nutrition Although chemists[?] again studied this yellow material in 1925 and described some of its properties its biochemical nature re

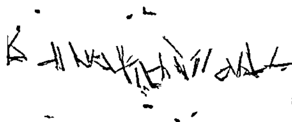


Fig 38 Crystalline riboflavin (courtesy of Merck and Co)

mained to be disclosed through a different source In 193 Warburg and Christian [?] described a new yellow enzyme which they obtained from the aqueous extract of bottom yeasts It proved to be one of the most ubiquitous of the enzymes concerned in cellular respiration and these investigators later separated this yellow enzyme into a protein component and a pigmented portion and noted that neither alone was active In 1933 Kuhn and his co workers isolated the pigment from natural sources and in 1935 Karrer and his collaborators [?] and Kuhn and his associates [?] independently synthesized riboflavin

Chemistry and Physiology

Riboflavin crystallizes in fine yellow needles which melt at 282° C (Fig 38) The structural formula of riboflavin is shown in Figure 39 The pure compound is only slightly soluble in water and ethyl alcohol and is very soluble in alkali solutions It is insoluble in acetone ether

Toxicity

Nicotinic acid, in the amounts recommended for therapy, is not toxic although it and all related compounds containing the free radical produce vasodilation in the skin and an increase in skin temperature as already illustrated by Figure 36

the absence of substituents in both positions is accompanied by toxicity An unsubstituted group in the three position also is necessary for activity

Riboflavin is a combination of d ribose and isoalloxazine The phosphoric acid ester of riboflavin unites a specific nonactive bearer protein to form the yellow enzyme In the presence of an activating enzyme from yeast (Zwischenferment) and a thermostable coenzyme (now identified as coenzyme II triphosphorpyridine nucleotide) the yellow enzyme is capable of oxidizing Robinson's hexose monophosphoric ester The following scheme has been postulated for the action of this system

(1) coenzyme + hexose monophosphoric acid —Zwischenferment→ reduced coenzyme phosphohexonic acid

( ) reduced coenzyme + yellow enzyme ——→ coenzyme + reduced yellow enzyme

(3) reduced yellow enzyme + molecular oxygen ——→ H O + yellow enzyme

This system in contrast to other well known oxidation reduction systems is not poisoned by hydrocyanic acid or carbon monoxide Since the coenzyme is alternately reduced and oxidized by the yellow enzyme and the yellow enzyme itself is reversibly oxidized and reduced only a very small amount of both of these substances is required for the reaction

In similar enzyme systems the flavoprotein is concerned with oxidation of amino acids It combines with phosphoric acid ribose and adenine to form a d amino oxidase A similar dinucleotide has been described which catalyzes the oxidation of aldehydes and lactic acid Another flavoprotein enters the metabolism of xanthines as an oxidase A number of flavoproteins have been described chemically some are inactive and the biological importance of others has not been established

Riboflavin occurs naturally in three forms as riboflavin per se as riboflavin 5 phosphoric acid and as riboflavin adenine dinucleotide It may be absorbed easily by the intestine in any of these forms The transformation of riboflavin to its phosphoric acid ester and the dinucleotide is a general cellular reaction Human blood cells for example can make the synthesis *in vivo* or *in vitro*, but the plasma cannot This means that riboflavin can be administered parenterally and we often do this

It would seem that the liver and kidney are the organs most concerned with the use of riboflavin and other substances to form specific enzyme systems Riboflavin is excreted chiefly in the feces When the diet is low in riboflavin practically no riboflavin is excreted in the urine,

benzene and choroform The water solution is of greenish-yellow color and has an intense yellow-green fluorescence which disappears with the addition of either acids or alkalis Light slowly destroys the vitamin activity The decomposition is influenced also by temperature and by the hydrogen ion concentration It has a relatively high thermostability

Under ultra-violet light riboflavin emits a blue green fluorescence It is on this property that the fluorometric quantitative determination of the substance depends A second accurate method of quantitation is based upon the conversion of riboflavin to lumiflavin by exposure to light in alkaline solution The amount of lumiflavin then can be deter

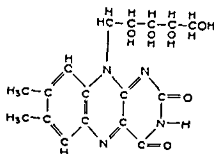


Fig 59 Structural formula of d riboflavin (6,7 dimethyl 9 (1 d ribityl) isoalloxazine)

mined colorimetrically A microbiological assay measures the acid production by *Lactobacillus casei*, this is proportional to the amount of riboflavin present in the system

Riboflavin takes part in many different enzyme systems in the tissues Each system consists of an apoenzyme and a coenzyme The apoenzyme is a specific protein or the "Zwischenferment" The coenzyme constitutes the prosthetic group of the enzyme system and riboflavin is an integral part of its constitution The same coenzyme can serve as the prosthetic group of a number of different apoenzymes

The two coenzymes containing riboflavin are (1) riboflavin 5 phosphoric acid (riboflavin mononucleotide) and (2) riboflavin adenine dinucleotide Riboflavin acts on the various enzyme systems by reversibly accepting and donating two atoms of hydrogen This is accomplished by the addition of the hydrogen to the one and ten positions of riboflavin Riboflavin is the only naturally-occurring flavin with vitamin B activity Many flavin compounds have been prepared synthetically and shown to have vitamin activity Generally speaking substitution in the six or seven position is necessary for vitamin activity and

tongue have been made using the slit lamp biomicroscope These reveal the nonspecific changes so often accompanying inflammation and atrophy Although our knowledge of the pathological physiology is far from complete it is believed that the cornea and other relatively avascular tissues are dependent to a great extent on the flavoprotein for normal respiration This may explain the vascularization around the cornea in individuals which is relieved by riboflavin

Until recently little precise scientific knowledge has existed in regard to the assumption that congenital anomalies may occur as a result of a deficiency *of riboflavin in the maternal diet Warkany and associates* [38-43] have shown that female rats on restricted diets give birth to young with skeletal defects Malformations occurred in the extremities the jaw and the ribs and there was a constant type of cleft palate These authors have shown that the malformations could be prevented completely by giving riboflavin One of the most interesting aspects of these studies has been the determination of the actual period of embryonic development in which the deficiency of riboflavin results in abnormal tissue differentiation They found that the mother rat still could produce normal young if the deficient diet was corrected on the twelfth day of gestation The thirteenth day was the critical day adding the supplement on the fourteenth day or any day thereafter failed to protect the young The implications of these dramatic experiments with respect to maternal human nutrition are tremendous It would seem that it is not enough that the mother be able to conceive, she must have adequate nutrients for normal differentiation and for normal reproduction

It is highly probable that riboflavin may constitute a part of many enzymes other than Warburg's yellow enzyme xanthine oxidase and d aminoacid oxidase This postulate might explain the all too frequent cheilosis which is not healed by riboflavin Under such circumstances it may be that the system of hydrogen carriers and acceptors is disrupted at a point close to the active position of riboflavin and that similar pathological lesions are produced even when the supply of riboflavin is adequate or excessive There is some suggestion that pyridoxine (vitamin B_6)[279] or iron may fit into such auxiliary systems

The theory that the ocular lesions of riboflavin deficiency result from anoxia has been advanced [29] the engorgement of the conjunctivae and limbal vessels may be considered an inadequate attempt to supply the tissues in this area with adequate oxygen Thus one might expect a deficiency of almost any enzyme to produce similar ocular signs It is equally possible however that riboflavin may aid in the formation of

although it is still found in the feces. An increase in the riboflavin intake of human beings is followed rapidly by an increase in the urinary output. The animal organism apparently has no special storage organ for riboflavin although the blood level is maintained in spite of lesions in man. Larger concentrations are found in the liver and in the kidney, although a large intake of riboflavin does not increase its content to any great extent. Even when animals die from lack of this vitamin their tissues still contain considerable amounts, often as much as one third of the normal level. No substantial decrease of the riboflavin content of the blood and muscles could be observed in man even though they had clinical lesions.[31]

If the intake from the gastrointestinal tract is increased greatly there is only a slight increase in the amount stored. As long as the diet is adequate, riboflavin is excreted in the urine. On a low dietary intake the excretion exceeds the intake but gradually decreases. The body clings tenaciously to its stores of riboflavin. Axelrod, Spies and Elvehjem[2] could not detect a correlation between the amount of a test dose of riboflavin retained and the daily urinary riboflavin excreted in human beings. They did produce uncomplicated riboflavin deficiency in the dog, however, in which the degree of retention of a test dose of riboflavin was found to be a measure of the riboflavin deficiency.

Riboflavin is distributed so widely that it seems that each animal and plant cell contains small amounts. The amount in the seeds of plants is small but increases rapidly during germination. The richest source of riboflavin is certain fermentation bacteria. Yeast contains considerable amounts. The liver, kidney and heart contain about ten to thirty times the amount found in muscles. The retina of the eyes of many species of animal contains large quantities of riboflavin. Riboflavin tends to be found in the free form in human milk, in the urine and in the retina.

Canning processes cause the loss of from 12 to 67 per cent of the riboflavin in foods. Ordinary cooking, however, destroys but little and the only loss of magnitude occurs in the event that water, in which food has been boiled, is discarded. Freezing of foods for storage does not alter appreciably their riboflavin content.

Pathological Physiology

There has been so little investigation of the histological changes in human tissues in riboflavin deficiency that a pathological description is not available. Studies of gross living material, particularly the eye and



Fig 40 Cheilosis from riboflavin deficiency

choline esterase and through its action on acetylcholine and the autonomic nervous system effect conjunctival vasodilatation

Since it was demonstrated that riboflavin is synthesized by bacteria in the rumens of animals, it has been suspected that this might occur in the intestinal tract of man There has been some indirect evidence to substantiate this hypothesis[10] The authors have been unable to determine the amount of riboflavin produced by intestinal bacterial synthesis The type of bacterial flora and the quality of the diet are important but it has not been determined whether or not the body can utilize the riboflavin present in viable bacteria

SYMPTOMATOLOGY

Perhaps the most characteristic clinical sign in riboflavin deficiency is an angular stomatitis which is called cheilosis[11] The earliest change is a paleness of the lips particularly at the angles but not the moist area of the buccal mucosa The pallor usually continues for days and is followed by maceration and piling up of whitish tissue on a pink background Superficial fissures may invade the site of the natural wrinkles at the corners of the mouth The macerated lesions subsequently become dry, and a yellowish crust, which forms at the angles can be removed without causing bleeding As the disease progresses, the fissures in the corners of the mouth tend to become deeper and extend to the cheek They may extend within the mouth so that the constantly irritated angles become raw bleeding areas with crusts or scabs Such lesions are sometimes very painful in the acute stage Frequent recurrences may result in the formation of a cicatrix giving the affected area an atrophic appearance Cheilosis usually occurs at both angles of the mouth but sometimes only one angle is involved (See Fig 40) Furthermore there may be a difference in severity of the lesions at the two angles of the mouth and in occasional cases the lesion at one angle progresses while the other regresses Another alteration occurs, usually in the inner surface of the lower lip apparently with the shedding of superficial epithelium the mucous border becomes a brilliant red On close examination one finds this to be caused by increased visibility of a myriad of minute dilated vessels This rarely is associated with burning of the lips and tongue The lesions of the lips and the angles of the mouth often heal spontaneously in the winter and summer and break down in the spring and fall, and persons whose lips have undergone these changes repeatedly,

show scarring in the angles of the mouth and mottling of the vermilion border of the lips

Such pathological changes at the angles of the mouth have been called perleche' which means to lick intensively' Epidemics of perleche have been described particularly in children s institutions In one such epidemic Finnerud[12] called attention to a seborrhoeic dermatitis-like eruption of the face in 18 of 100 children with perleche In 1944 he reviewed the etiology of perleche and emphasized its polyetiological nature[13] Such lesions of the angles of the mouth which heal with riboflavin also yield smears and cultures positive for yeast fungi and bacterial organisms such as staphylococci streptococci and Vincent s organisms

Cheilosis of a mechanical etiology must be differentiated from that caused by riboflavin deficiency This type has been studied by Ellenberg and Pollack[14] and by Mann and Spies[24] and it has been related directly to a decrease in the vertical dimension of the face in many instances due to ill fitting dentures only one denture or none at all Thus, consumption of an adequate amount of a varied diet often was impossible When these patients were given riboflavin there was an amelioration of the cheilosis but the lesions did not disappear With sagging of the facial muscles and the resultant fissures at the angles of the mouth saliva readily leaks into the intertriginous areas and maceration and infection result It is necessary to restore adequate dental function and a normal contour of the face in order to facilitate the healing of the lesions in these persons It is only under such circumstances that they can ingest the foods necessary to maintain optimal nutrition

Often the prominence of the papillae is reduced and the tongue has a smooth appearance It may be purplish red or magenta in color Irregular patches of erythema may be present but they are not as fiery red as they are in nicotinic acid amide deficiency Frequently the glossitis of pellagra obscures that of riboflavin deficiency and it is not until the pellagrous erythema has blanched following the administration of nicotinic acid that the underlying purplish color characteristic of riboflavin deficiency can be seen Clinical trial first with nicotinic acid and then with riboflavin often is necessary in order to distinguish the glossitis of pellagra from the glossitis of riboflavin deficiency

The first statement in regard to certain eye symptoms arising in persons with riboflavin deficiency is that of Spies Bean and Ashe in 1939[246] They described a series of symptoms which disappeared within forty-eight hours after a single injection of riboflavin and returned within ten

and vision improved. Although 84 per cent of the patients subsequently had recurrences this is attributed to cessation of therapy and a return to the previous diet which was inadequate in riboflavin.

It must be emphasized that the differentiation of these superficial lesions of the eye from other types of conjunctivitis and keratitis is both difficult and uncertain. It seems that many other varieties of conjunctivitis also may be benefited by the parenteral administration of riboflavin which suggests that this vitamin may play a routine part in such inflammations.

Diagnosis

In making a diagnosis the physician should keep in mind that riboflavin deficiency may occur in either sex at any age and in any race, that it usually *occurs following subsistence for months or years on a diet* deficient in riboflavin and that it is especially common among those whose diets are inadequate. It may occur, however, as a result of a *metabolic complication of some other disease state* and in such cases it is referred to as secondary riboflavin deficiency. The physiological possibilities for the induction of a secondary deficiency may be listed briefly as follows: (a) decreased intake, (b) decreased absorption, (c) increased excretion, (d) increased requirement, (e) decreased utilization, (f) increased destruction.

In a report describing observations on 500 selected cases of riboflavin deficiency, Spies, Perry, Cogswell and Frommeyer[43] found that the dietaries of these patients supplied only one third of the allowance of riboflavin recommended by the Food and Nutrition Board of the National Research Council (see Fig. 41).

What should *constitute the exact criteria for the diagnosis of human* riboflavin deficiency is almost impossible to estimate from the various reports. Sebrell[4] has summarized his concept as follows:

(1) Ocular lesions consisting usually *of a vascularizing keratitis* with photophobia, dimness of vision, severe injection of the vessels of the fornix and sclera, burning of the eyes, lacrimation, and in severe cases opacities of the cornea; (2) oral lesions consisting usually of linear fissures in the angles of the mouth, a reddened shiny denuded appearance of the lower lip and a flattening of the papillae of the tongue which becomes magenta red in color; (3) dermal lesions consisting usually of seborrheic accumulations in the folds of the skin especially in the nasolabial folds, around the eyelids, on the ears and

to twenty days, if the deficient diet was continued The syndrome was greatly amplified by Spies, Vilter and Ashe[17] the same year They called attention to ocular manifestations of riboflavin deficiency in human beings These manifestations included bulbar conjunctivitis, dilatation of the conjunctival vessels burning of the eyes, lacrimation, failing vision and extreme photophobia All the patients studied were known to have been on a riboflavin deficient diet, and their symptoms disappeared following riboflavin therapy Soon many investigators reported studies on riboflavin deficiency, and the next year Kruse, Sydenstriker, Sebrell and Cleckley[218] reported on nine patients and stated that the principal manifestation was keratitis Later that year these investigators reported that by means of the slit lamp they had found vascularization of the cornea They stressed particularly the superficial vascularization of the cornea and the finding of interstitial keratitis Unfortunately these investigators apparently did not examine the corneas of a large number of patients for today there is much controversy on the subject and a wide divergence of opinion Many ophthalmologists have refused to accept the specificity of these ocular lesions

A study of 500 patients with the ocular manifestations of riboflavin deficiency by Spies, Perry, Cogswell and Frommeyer[19] shows that these lesions frequently occurred in the absence of cheilosis or vice versa The visual symptoms in practically all the patients were heralded by a feeling of dryness of the eyes which was followed by burning and itching and sometimes by photophobia and lacrimation In some cases conjunctivitis was the sole manifestation and was shown by increased visibility of the vessels of both the bulbar and palpebral conjunctivae, apparently due to congestion and dilatation Small vessels were observed to encroach on the cornea at the scleral corneal junction Interstitial keratitis was observed in 60 per cent of the patients and corneal ulceration in at least one eye in 53 per cent In all cases an effort was made to eliminate other etiological disorders such as vernal conjunctivitis, foreign bodies in the cornea xerophthalmia and such diseases of the uveal tract as iritis due to syphilis tuberculosis and rheumatic fever

Within forty eight hours after beginning therapy there was some subjective improvement in all the patients Improvement was volunteered in 80 per cent of the cases Within this period a diminution in the calibre of the dilated vessels in the eyes and a striking decrease in the photophobia and corneal ulcerations were observed Accompanying this improvement was a decrease of hemolytic staphylococci streptococci and xerosis bacilli in the exudate from the eyes Relief of pain occurred

in some cases comedones and a sharkskin-appearing lesion on the nose and over the malar eminences In some cases the seborrheic dermal lesions may be extensive and may involve other regions of the body

In the absence of characteristic lesions the recognition of riboflavin deficiency is difficult An appraisal of the dietary of the patient is helpful but not an infallible guide The scars of old cheilosis should arouse suspicion In the prodromal period prior to the appearance of typical lesions most of the subjective symptoms result from depletion of niacinamide and thiamine stores Neither at this period nor later when the lesions are advanced is there a consistently accurate laboratory test to determine the adequacy or inadequacy of the stores of riboflavin

A tentative diagnosis is warranted in the presence of cheilosis with angular stomatitis engorgement of pericorneal vessels and concommitant subjective symptoms of photophobia burning and dimness of vision Riboflavin deficiency should be suspected in the person who presents a magenta tongue or the greasy, scaly dermatitis in characteristic areas about the face and the sharkskin appearance of skin over the nose and malar prominence In examining the tongue however it should be kept in mind that forceful protrusion results in compression of the ranular veins and in congestion and cyanosis Therefore the magenta hue should be observed in the tongue at rest within the mouth

The therapeutic test substantiates the diagnosis Healing of the angles of the mouth and the tongue usually is initiated after from three to six days of specific therapy Subjective improvement in the ocular lesions usually is noticeable in 24 hours if large doses are given although objectively there may be little change for from two days to a week Complete healing of the eye and skin lesions extends over a period of several weeks and the conjunctivitis is prone to relapse when treatment is discontinued

Prevention and Treatment

Riboflavin deficiency can be prevented either by the use of synthetic riboflavin or by the consumption of foods rich in riboflavin The practicing physician is urged to read the sections on vitamin B_1 and nicotinic acid for the dietary management and general recommendations for the prevention and treatment of nutritional deficiencies Single vitamin deficiencies occur rarely and despite the fact that riboflavin deficiency may dominate the clinical picture it is unlikely that the physician will see a patient who has uncomplicated riboflavin deficiency There are no defi-

RECOMMENDED DIETARY ALLOWANCES REVISED 1945[1]

(AMOUNTS PER DAY)

Food and Nutrition Board National Research Council

	Calories	Protein grams	Calcium grams	Iron mg	Vitamin A I U[2]	Thiamine mg[3]	Riboflavin mg[3]	Niacin (Nicotinic acid) mg[3]	Ascorbic acid mg	Vitamin D I U
Man (154 lb 70 kg)										
Sedentary	2500	70	0.8	12[4]	5000	1.2	1.6	12	75	[5]
Moderately active	3000	70	0.8	12[4]	5000	1.5	2.0	15	75	[5]
Very active	4500	70	0.8	12[4]	5000	2.0	2.6	20	75	[5]
Woman (123 lb 56 kg)										
Sedentary	2100	60	0.8	12	5000	1.1	1.5	11	70	[5]
Moderately active	2500	60	0.8	12	5000	1.2	1.6	12	70	[5]
Very active	3000	60	0.8	12	5000	1.5	2.0	15	70	[5]
Pregnancy (latter half)	2500[6]	85	1.5	15	6000	1.8	2.5	18	100	400 to 800
Lactation	3000	100	2.0	15	8000	2.0	3.0	20	150	400 to 800
Children up to 12 yrs[7]										
Under 1 yr[8]	100/2.2 lb (1 kg)	3.5/2.2 lb (1 kg)	1.0	6	1500	0.4	0.6	4	30	400 to 800
1–3 yrs (9 lb 13 kg)	1200	40	1.0	7	2000	0.6	0.9	6	35	400
4–6 yrs (42 lb 19 kg)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
7–9 yrs (55 lb 25 kg)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
10–12 yrs (75 lb 34 kg)	2500	70	1.2	12	4500	1.2	1.8	12	75	400
Children over 12 yrs[7]										
Girls 13–15 yrs (108 lb 49 kg)	2600	80	1.3	15	5000	1.3	2.0	13	80	400
16–20 yrs (119 lb 54 kg)	2400	75	1.0	15	5000	1.2	1.8	12	80	400
Boys 13–15 yrs (103 lb 4 kg)	3 00	85	1.4	15	5000	1.5	2.0	15	90	400
16–20 yrs (141 lb 64 kg)	3800	100	1.4	15	6000	1.8	2.5	18	100	400

[1] Te tat e goal towa d which to aim in planning practical dietaries can be met by a good diet with a variety of natural foods. Such a diet will also provide other minerals and vitamins the requirements for which are less well known.

[2] The allowance depends on the rel t e amounts of vitamin A and carotene. The allowances of the table are based on the p m e that approximately t o-thirds of the vitamin A value of the a ge d t th s co t y nt but d by carotene and that carotene is h lf o l ss tha h lf t l e f vitamin A.

[3] For adults (except pregnant ... lactating women) ... g d t supply ... 2 000 calories or less such as reducing diets the allowances of thiamine riboflavin and niacin may be 1 mg 1.5 mg and 10 mg respectively. The fact that figures a give for different calorie levels fo thiamine riboflavin and niacin does t imply that e an estimate the requirement of the fact s ... 500 calories b t they are added merely for simplicity of calculation. Other members of the B complex also are required th ugh no ... can be g n Foods ... g d q ... boff a d ... n ll t nd to supply ... of t ... g B ... s

[4] Tl ... d nce th t tl ... m l ... d lt ... d l ... o no ... n

Fig 41 Recommended dietary allowances revised 1945 (amount per day) Food and Nutrition Board National Research Council

in some cases comedones and a sharkskin appearing lesion on the nose and over the malar eminences. In some cases the seborrheic dermal lesions may be extensive and may involve other regions of the body.

In the absence of characteristic lesions the recognition of riboflavin deficiency is difficult. An appraisal of the dietary of the patient is helpful but not an infallible guide. The scars of old cheilosis should arouse suspicion. In the prodromal period prior to the appearance of typical lesions most of the subjective symptoms result from depletion of niacin amide and thiamine stores. Neither at this period nor later, when the lesions are advanced, is there a consistently accurate laboratory test to determine the adequacy or inadequacy of the stores of riboflavin.

A tentative diagnosis is warranted in the presence of cheilosis with angular stomatitis, engorgement of pericorneal vessels and concommitant subjective symptoms of photophobia, burning and dimness of vision. Riboflavin deficiency should be suspected in the person who presents a magenta tongue or the greasy scaly dermatitis in characteristic areas about the face and the sharkskin appearance of skin over the nose and malar prominence. In examining the tongue, however, it should be kept in mind that forceful protrusion results in compression of the ranular veins and in congestion and cyanosis. Therefore the magenta hue should be observed in the tongue at rest within the mouth.

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nite lesions which are pathognomonic of riboflavin deficiency The cheilosis or the ocular manifestations may or may not be due to riboflavin deficiency The authors give from 5 to 50 mgm of riboflavin, but as a rule they find that 10 mgm daily is adequate for the average case It may be given orally intravenously or intramuscularly Subcutaneous

FOODS AS SOURCES OF

RIBOFLAVIN

(VITAMIN G)

Milk is the most important common source of riboflavin This vitamin is not readily destroyed by heat but it may be lost by extraction in water during cooking and by prolonged exposure to light

CONTRIBUTION OF SELECTED SERVINGS OF A FEW FOODS AS PERCENTAGES OF ADULT MALE ALLOWANCE (2.7 MILLIGRAMS)

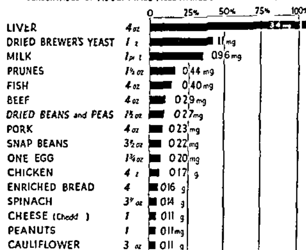


FIG 42 Foods as sources of riboflavin (Vitamin G)

administration causes considerable pain The symptoms are relieved much more quickly by parenteral than by oral therapy Cheilosis corneal ulceration corneal vascularity photophobia and non infectious conjunctivitis respond rapidly to treatment with riboflavin if they are due to a deficiency of riboflavin The tendency of lesions to reappear after cessation of treatment is common and may occur even when the

dietary is at an optimal level Consequently frequent observation is necessary for a long period of time Should relapse occur the reinstatement of therapy usually affords prompt amelioration of the symptoms The authors wish to stress however that neither the cheilosis nor the dilated blood vessels of the eye are pathognomonic of riboflavin deficiency They may arise from other causes in which case riboflavin will not correct them

Toxicity

Riboflavin is practically non toxic Mice fed over 5 000 times the daily requirement do not show any pathological symptoms The authors have given 100 mgm daily for three months to patients without any ill effects resulting

FOLIC ACID

History

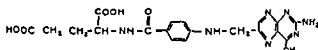
The finding of a synthetic chemical compound of known molecular structure, which is effective in treating persons with nutritional macrocytic anemia, pernicious anemia and the macrocytic anemia of sprue is a medical event of great importance. This substance, commonly called "folic acid", is the newest member of the vitamin B complex. The name folic acid originally was given to a mixture of substances obtained in nearly pure form from spinach by Mitchell, Snell and Williams.[51] Their concentrate was shown to support growth for two organisms frequently used in microbiological investigations, *Lactobacillus casei* and *Streptococcus faecalis*. Strictly speaking, the *Lactobacillus casei* factor, or pteroylglutamic acid as it properly is termed chemically, should not be called folic acid. The term has become so widely used, however, that it will be regarded as synonomous with the *Lactobacillus casei* factor or pteroylglutamic acid.

This substance gradually emerged as a separate entity as the result of the work of many investigators in many laboratories over a period of eight years. In 1938 Stokstad and Manning reported that a purified diet even when supplemented with crude concentrates containing thiamine, riboflavin, niacin, pyridoxine and pantothenic acid would not satisfy the nutritional requirements of chicks, but that the missing factor was supplied by the addition of concentrates from yeast and alfalfa.[53] In 1940 Hogan and Parrott[54] reported that an anemia developed in chicks on a purified diet unless they were given an unidentified factor which could be supplied with suitable preparations obtained from liver. The same year Snell and Peterson[55] showed that an unidentified water soluble factor, "the yeast norite eluate factor", was necessary for the growth of *L. casei*. Later Hutchings and his associates[56] observed that, when the factor was concentrated from extracts prepared from liver, the potency in promoting the growth of chicks on a purified diet was found to increase simultaneously with the potency as measured by *L. casei* factor. This proved to be similar to the "folic acid" obtained from spinach by Mitchell, Snell and Williams. Minute quantities of the *L. casei* factor were obtained in crystalline form from liver by Pfiffner and his associates[57] and from liver and yeast by Stokstad.[58] In 1945 it was synthesized by Angier and his co-workers[59] and a few months later they published its structural formula (see Fig. 43).[60] A review of many

aspects of the studies which led to the isolation and synthesis of foli acid and studies on its clinical use has been published recently by Berry and Spies [61] and by Spies [262]

Chemistry and Physiology

As can be seen from the formula (Fig 43) folic acid contains a pteridine ring and one molecule each of para aminobenzoic acid and



N (4 {[(2-amino-4 hydroxy-6 pteridyl)methyl] amino} benzoyl] glutamic acid

Fig 43 Structural formula of the liver *L casei* factor

glutamic acid Pteroic acid and glutamic acid are of great interest because of their chemical relationship to the folic acid molecule As can be seen from their chemical formula in Figs 44 and 45, pteroic acid differs from folic acid pteroylglutamic acid by the absence of one molecule of glutamic acid In their studies on the synthesis of folic acid Angier and his associates found that by substituting p aminobenzoic acid

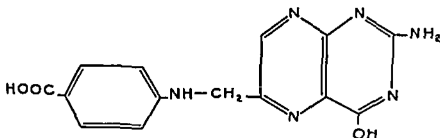


Fig 44 Structural formula of petroic acid

for p aminobenzoyl 1(+) glutamic acid in the process a compound was produced which had growth activity for *Streptococcus faecalis* but not for *L casei* and the chick The term assigned to this compound is pteroic acid In contrast to pteroylglutamic acid, which is a potent hemopoietic agent pteroic acid and glutamic acid do not show any hemopoietic activity when administered either separately or together It must be assumed therefore that these substances must be prefabricated to form

pteroylglutamic acid before they can be utilized by the body for blood regeneration

Folic acid is a bright yellow substance which crystallizes as is shown in Fig 46 It is destroyed fairly rapidly by heating with dilute mineral acids, and sunlight has a destructive effect on a solution of folic acid It occurs in nature in a free form and also as a part of various complexes The following substances have been isolated in crystalline form, (1) vitamin B_c, (2) *Lactobacillus casei* factor from liver, (3) *Lactobacillus*

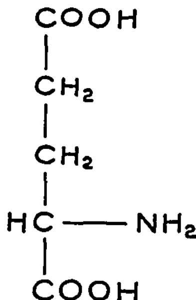


Fig 45 Structural formula of glutamic acid

casei factor from yeast, (4) another *Lactobacillus casei* factor isolated from a fermentation residue and (5) vitamin B_c conjugate Vitamin B the *L casei* factor from liver and the *L casei* factor from yeast are identical with the synthetic product described by Angier and his associates This compound, folic acid or pteroylglutamic acid, contains one molecule of glutamic acid In contrast the conjugated *L casei* factor isolated from the fermentation residue yields three molecules of glutamic acid and is called pteroyltriglutamic acid The vitamin B_c conjugate contains 7 molecules of glutamic acid and is termed pteroylheptaglutamic acid The structural formulas of these substances could be written as is shown in Fig 47 although the precise structure is not known at this time These substances are somewhat effective in producing a hemopoietic response in certain types of macrocytic anemia in relapse but less effective per

unit of weight than is folic acid[263] Within 4 hours after the administration of pteroylglutamic acid to persons with pernicious anemia there is a great increase in the urinary excretion of this substance whereas the administration of vitamin B_c conjugate is not followed by a great increase in the amount of folic acid excreted in the urine of some patients with pernicious anemia (Fig 48)

Whether or not most animals can synthesize folic acid has not been determined The relative scarcity of it in animal tissues suggests that if

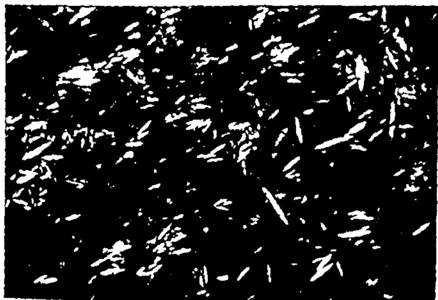


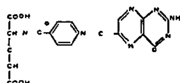
Fig 4(Microphotograph showing crystalline folic acid (courtesy of Lederle Laboratories Inc)

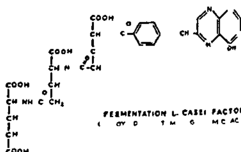
it is synthesized only small quantities of it are produced or only small amounts are stored It is possible that the bacteria normally present in the intestinal tract of some animals such as the rat may synthesize considerable quantities Experimentally folic acid has been found to be essential for the proper nutrition of a variety of micro organisms and laboratory animals either as a growth promoting or a hemopoietic stimulating factor or both [91 28] Although its role in human nutrition is not clear its effectiveness in the treatment of macrocytic anemias in relapse has been established

Pteroylglutamic acid is distributed widely in both plant and animal

tissues At the present time the distribution of folic acid in foods usually is studied by microbiological assays Olson, Burns and Elvehjem[61] have classified foods assayed for their folic acid content by such methods as follows

1 Very high in folic acid content deep green leafy vegetables, liver





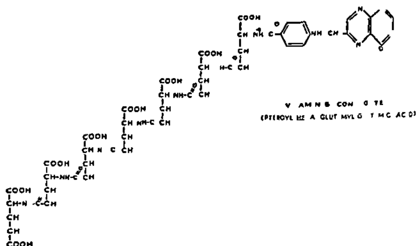


Fig 47 Suggested structural formulae for fermentation *L casei* factor and vitamin B_c conjugate

2 High in folic acid content fresh green vegetables cauliflower and kidney

3 Medium in folic acid content beef, veal dry breakfast cereals from wheat

4 Low in folic acid content root vegetables, tomatoes cucumbers light green leafy vegetables, bananas pork ham, lamb cheese milk, dry cereals prepared from rice or corn and many canned foods

Pathological Physiology

Folic acid has a profound effect on the bone marrow of persons with certain types of macrocytic anemia in relapse Nevertheless, it cannot

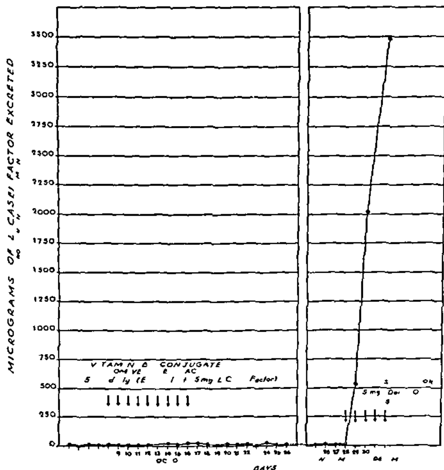


Fig 48 Chart showing excretion in the urine of folic acid after giving to a patient with nutritional macrocytic anemia 5 c c of vitamin B conjugate daily for 9 days

be said that the megaloblastic arrest of the bone marrow was caused by a folic acid deficiency Liver extract and ventriculin produce a similar

therapeutic effect, yet there is much reason to believe that folic acid is different from the anti anemic factor or factors in these substances

By using the sternal puncture in patients under investigation, it is possible to follow the action of folic acid step by step in the bone marrow In contrast to the peripheral blood picture, where changes first become appreciable several days after the onset of treatment profound transformations of the bone marrow occur earlier Reticulocytosis can be detected in the bone marrow, sometimes as early as the second day The number of megaloblasts and early erythroblasts decreases progressively and the late erythroblasts and normoblasts increase Eventually the normal ratio of nucleated red blood cells and white blood cells of the marrow is re-established In the following series of studies done at the time the patient was admitted to the hospital and twice during therapy one sees a disappearance of the megaloblastic arrest, and the bone marrow becomes normal

Bone marrow study on admission

Sternal bone marrow was obtained by means of the Turkel trephine

[illegible]00 W B C were counted

Cells	*Number*	*Percent*
PMN	120	60
Metamyelocytes	36	8
C myelocytes	2	1
B myelocytes	0	0
A myelocytes	0	0
Basophils		1
Basophilic myelocytes	0	0
Eosinophils	4	2
Eosinophilic myelocytes	10	5
Plasma cells	[illegible]	1
Megakaryocytes	0	0
Primitive cells	4	[illegible]
Total	[illegible]00	100
Megaloblasts	1[illegible]	
Early erythroblasts	6	
Late erythroblasts	9	
Normoblasts	15	
Total	4[illegible]	

Impression Hyperplastic bone marrow with megaloblastic arrest arrest

Bone marrow study made on the 51st day of treatment showed

Cells	*Number*	*Percent*
PMN	86	43 0
Metamyelocytes	50	5 0
C myelocytes	[illegible]	1 5
B myelocytes	4	0
A myelocytes	5	
Basophils	1	0 5
Basophilic myelocytes	1	0 5
Eosinophils	9	4 5
Eosinophilic myelocytes	35	17 5
Plasma cells		1 0
Megakaryocytes	1	0 5
Primitive cells	[illegible]	1 5
Total	00	100
Megaloblasts	6	
Early erythroblasts	11	
Late erythroblasts	0	
Normoblasts	109	
Total	146	

Impression A reactive bone marrow which shows a good response to therapy There is still some evidence of megaloblastic arrest

Bone marrow study made on the 74th day of treatment showed

PMN	94	47 0
Metamyelocytes	54	7 0
C myelocytes	8	4 0
B myelocytes	5	5
A myelocytes		1 0
Basophilic myelocytes	1	5
Eosinophils	6	3 0
Eosinophilic myelocytes	17	8 5
Plasma	1	5
Megakaryocytes	1	5
Primitive	6	3 0
Lymphocytes	5	- 5
Total	00	100

Cells	*Number*	*Percent*
Megaloblasts	0	
Early erythroblasts	3	
Late erythroblasts	24	
Normoblasts	37	
Total	64	

Impression Essentially normal marrow except for an increased number of eosinophilic elements There has been a definite change toward normal since the 51st day of treatment

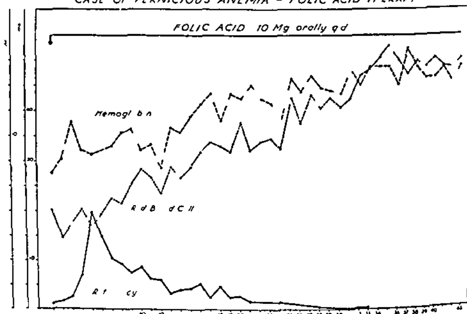


Fig 49 Chart showing changes in hemoglobin red blood cells and reticulocytes in patient with pernicious anemia following oral administration of folic acid

Reticulocytosis in the peripheral blood frequently is detected from about the third to the fifth day of therapy A peak is reached on the sixth to the tenth day The height of the rise varies from case to case depending upon the severity of the anemia the adequacy of the dose of folic acid and the presence or absence of complications In addition to the reticulocytosis there is a gradual increase in the number of red blood cells and in the hemoglobin (Fig 49) The thrombocytopenia and leukopenia, which so often are associated with macrocytic anemia, fre

quently are corrected by folic acid. The blood regeneration which follows folic acid therapy is comparable to that which follows therapy with reticulogen concentrated liver extract. Thymine (5 methyl uracil) another anti anemic substance likewise produces blood regeneration[64] but the response is of a lower order than that which follows a potent liver extract or folic acid as can be seen in Fig 50. Furthermore the large amount of thymine necessary to produce a therapeutic response up to 15 grams daily makes it impractical as a therapeutic substance although it is of great scientific interest.

SYMPTOMATOLOGY

Since it is not known that such a thing is a specific deficiency of folic acid exists in human beings the symptomatology of a folic acid deficiency in man cannot be described. Nevertheless the judicious administration of folic acid in suitable amounts is effective in treating Addisonian pernicious anemia nutritional macrocytic anemia and the macrocytic anemia of pellagra pregnancy and sprue. Some of the more pertinent findings are discussed under *Diagnosis* and *Treatment*.

DIAGNOSIS

Although the effectiveness of folic acid as a therapeutic agent in treating Addisonian pernicious anemia nutritional macrocytic anemia and the macrocytic anemia of pellagra pregnancy and sprue has been established[66–68] it cannot be overstressed that it is of no value in treating leukemia aplastic anemia or iron deficiency anemia. The anemia associated with liver disease usually does not respond to folic acid but in some cases it does. Nutritional leukopenia improves following treatment with folic acid but other types of leukopenia are not relieved. The physician who would prescribe folic acid should first make an accurate diagnosis.

The clinical syndromes of Addisonian pernicious anemia nutritional macrocytic anemia tropical sprue and the macrocytic anemia of pellagra and pregnancy *are indistinguishable either from examination of the* peripheral blood or from bone marrow studies. A characteristic feature of pernicious anemia is the absence of free hydrochloric acid in the gastric juice even after histamine stimulation. Many investigators agree that so called tropical and non tropical sprue are essentially the same

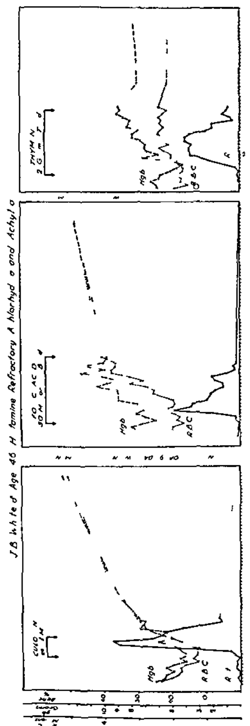


Fig. 50 Charts showing effects on blood of patient with pernicious anemia following administration in successive periods of reticulogen (concentrated liver extract) folic acid and thymine

disease The relationship of nutritional macrocytic anemia and sprue is more difficult to grasp Persons with either disease may have severe diarrhea but the characteristic diarrhea of sprue is the best differentiating feature and it is on the presence of this type of diarrhea that the diagnosis of sprue is based In sprue the stools usually vary in consistency from liquid to semi solid and in color from whitish yellow to yellowish green while in nutritional macrocytic anemia rarely are they foamy but they are foul in odor Bowel movements in sprue may occur from 3 to 20 or even 30 times a day tending to occur immediately after the patient eats food of any kind and the volume of the feces in 24 hours is greatly in excess of the normal volume Acid steatorrhea which almost invariably is present in sprue does not occur in nutritional macrocytic anemia The weight loss in sprue may be greater and less gradual than that which accompanies nutritional macrocytic anemia

Even when a considerable number of eminently qualified physicians examine a large group of patients with anemia a specific diagnosis is apt to be made in some cases whereas in others opinion is divided Frequently the physician may make a diagnosis the first time he examines the patient and observes him throughout a relapse of the disease but during a later recurrence he may change the diagnosis The author considers that the essential feature of the anemias which can be expected to respond to folic acid therapy, is megaloblastic arrest of the bone marrow associated with macrocytic anemia in persons who appear to have Addisonian pernicious anemia sprue nutritional macrocytic anemia or the macrocytic anemia of pellagra or pregnancy

When the physician realizes that patients with various clinical conditions respond to folic acid therapy it might seem academic to stress the necessity of making a specific diagnosis The prognosis and duration of therapy vary so greatly in the different types of macrocytic anemia however that no effort should be spared in obtaining as much precise and pertinent information as possible The finding of the specific effect of the folic acid molecule on the cells of the bone marrow and perhaps on other cells opens up a fresh and fertile field for the clinical investigator who must now re define the macrocytic anemias in the light of all the various loose threads which enter into the meshwork of their pathogenesis

Treatment

As yet no satisfactory explanation has been given for the fact that relatively large amounts of folic acid are required to produce a satisfac-

tory hemopoietic response Despite the many intensive clinical studies which have been made on folic acid as a therapeutic agent, the last word

RESPONSE OF A CASE OF SPRUE TO FOLIC ACID

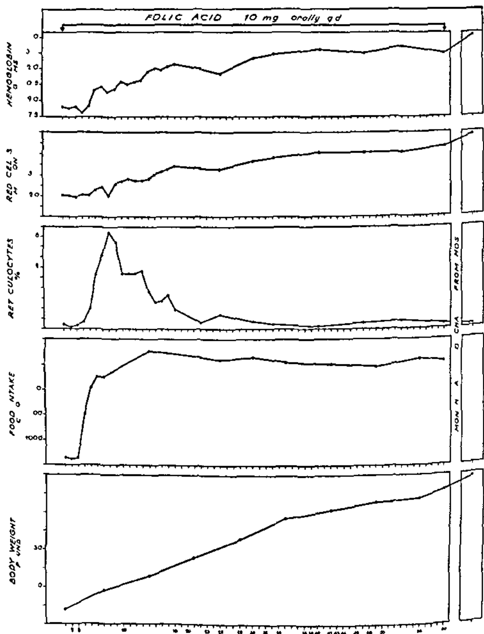


Fig 51 Response of a patient with sprue to administration of folic acid Vol I 948

on dosage cannot be stated definitely In most cases from 10 to [illegible]0 mgm daily in divided doses, given either orally or parenterally, is sufficient to



Fig 52 X ray showing intestinal pattern in sprue before treatment

induce a remission in persons with nutritional macrocytic anemia the macrocytic anemia of pregnancy pellagra, sprue and Addisonian pernicious anemia

The dramatic response of the bone marrow and peripheral blood

to folic acid in properly selected patients with macrocytic anemia in relapse is discussed and illustrated under *Pathological Physiology* The



Fig 53 X ray showing intestinal pattern of same patient with sprue as shown in Fig 52 before treatment

clinical response is equally dramatic At the time reticulocytosis begins the patients state voluntarily that they feel stronger Those who have lost their appetites experience a great increase in the desire for food, and

in many cases the food intake increases from less than 1 000 calories daily to between 3 000 and 4 000 calories within a day or two from the time reticulocytosis begins In cases of extreme weight loss such as that



Fig 54 X ray showing intestinal pattern of same patient with sprue as shown in Figs 5 and 53 before treatment

which occurs in sprue the gain in appetite and weight is particularly remarkable as can be seen in Fig 51 No adequate explanation can be given for the prompt improvement in the diarrhea in nutritional macro

to folic acid in properly selected patients with macrocytic anemia in relapse is discussed and illustrated under *Pathological Physiology* The



Fig 53 X ray showing intestinal pattern of same patient with sprue as shown in Fig 5 before treatment

clinical response is equally dramatic At the time reticulocytosis begins the patients state voluntarily that they feel stronger Those who have lost their appetites experience a great increase in the desire for food, and

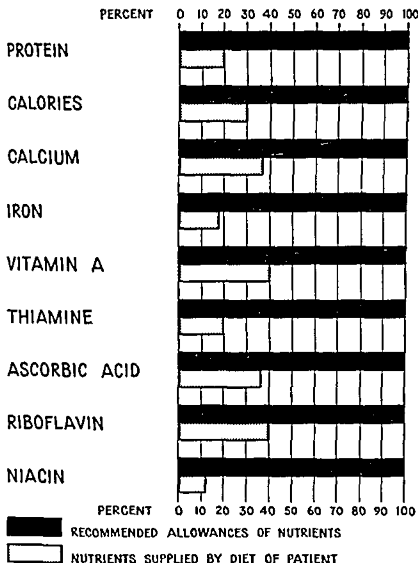


Fig 56 Chart showing nutrients supplied by diet of patient with chronic pellagra and nutritional macrocytic anemia contrasted to recommended allowance of nutrients

cytic anemia The stools may tend to become normal in frequency, color and volume

Folic acid therapy has a striking effect on the gastrointestinal tract



Fig 55 X ray of same patient with sprue as shown in Figs 52 53 and 54 six weeks after treatment with folic acid showing return to normal of intestinal pattern

of persons with tropical sprue [69] as can be seen in the illustrations Figs 52 53 54, 55 all made on the same patient The first three are taken before therapy and the fourth six weeks after folic acid therapy was initiated The abnormal dilatations and spasms seen in Figs 52 53 and

not only high in calories but is rich in all the essential nutrients In contrast some persons with pernicious anemia are obese and the caloric intake can be restricted without impairing the diet in respect to other nutrients Some patients may have renal insufficiency, diabetes or other diseases which require special dietary control In such cases the diet should be prescribed for the individual patient and planned with great care In some cases macrocytic anemia is accompanied by hypochromic anemia (iron deficiency anemia) Folic acid naturally will not replenish the deficiency of iron, and in such cases optimal doses of iron should be given

Toxicity

Apparently large amounts of folic acid can be given with impunity since one of the authors (T D S) has administered 400 mgm daily for 3 months without the patient s developing untoward symptoms

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54 disappeared as can be seen in Fig 55, which shows that the barium column is continuous and appears perfectly normal

The chief limitation of folic acid as a therapeutic agent is that it will neither prevent the development of acute or subacute combined system disease nor relieve it once it has developed [63, 0] Liver extract along with folic acid should be given in a dosage sufficient to relieve signs of acute or subacute degeneration of the spinal cord In patients, who are allergic to liver extract, folic acid is a valuable substitute unless the patient has neural degeneration In such cases folic acid therapy should be supplemented with the necesary amount of liver extract to bring steps to overcome the allergic action of the liver extract

In the treatment of macrocytic anemia correct diagnosis is basic The objective in the treatment of every patient is the restitution of the red blood cells, the white blood cells, the platelets and the hemoglobin the reduction of the red blood cells to normal size and the relief of all his symptoms with the result that he becomes completely rehabilitated In order to realize this objective it is necessary to make a thorough study of the patient and of his blood findings Once the diagnosis is made he should be given general therapeutic measures which will promote physical rest and mental serenity A proper diet should be stressed throughout the whole period of his convalescence and thereafter for the remainder of his life He should be treated with physiotherapy for any disturbances of gait and locomotion Transfusion should be given if necessary to save life Co-existing diseases should be treated and every effort should be made to eradicate them During convalescence the physician must remind patients with anemia to avoid unnecessary fatigue, since many of them are old and their heart function is impaired Dramatic recovery can be expected when folic acid is given promptly, efficiently and adequately to properly selected patients

Despite the fact that the blood levels improve following folic acid therapy, the general nutritional status of the patient frequently warrants particular attention The patient in severe relapse rarely is interested in food and it is unlikely that he has been consuming an adequate diet (See Fig 56) As a rule, the appetite increases tremendously after remission begins and it is not unusual for him to consume large amounts of food At this period it is of utmost importance to instruct every patient in regard to a proper diet Experience has taught us that there is a great variation in the individual needs of different patients The patient with sprue or pellagra usually is considerable underweight and has a deficiency of many nutrients Accordingly he may need a diet that is

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VITAMINS AND VITAMIN DEFICIENCIES (CONTINUED)

VITAMIN B_1

By TOM D. SPIES

TABLE OF CONTENTS

HISTORY

The modern era in the search for vitamin B_1 and substances that act similarly was initiated when Minot and Murphy [1] noted rapid improvement on feeding liver intensively to patients with pernicious anemia. It became evident that a potent liver extract would be more easily administered and a number of crude extracts were developed and later used widely for treating patients with pernicious anemia. Many liver extracts were manufactured and tested, and it soon became obvious that the positive hemopoietic effect varied according to the source of the material, the method of extraction and other unknown factors. An intensive search in many laboratories and clinics in various parts of the world was initiated to determine the exact nature of the potent substance or substances. Strandell and his associates in Scandinavia, Karrer and his

spectrographic analysis has shown the presence of cobalt in the vitamin B_{12} crystals The vitamin appears to be the first cobalt complex detected in human or animal tissues It appears to have six groups arranged about the cobalt atom and the bright red color of vitamin B_{12} appears to be associated with this cobalt complex X ray crystallography suggests that the molecular weight is about 1 500 to 1 750 The results of the American and British investigators although arrived at independently and often by different techniques have agreed remarkably Both groups

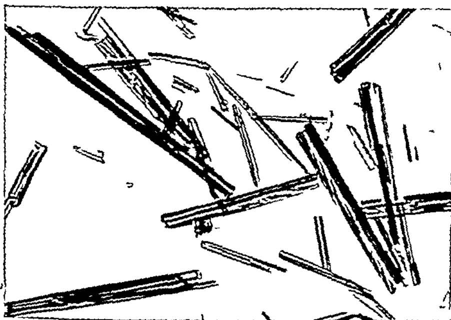


Fig 1 Microphotograph of vitamin B12 crystals (Courtesy of Dr Hans Molitor Merck Institute of Therapeutic Research)

not only have found the cobalt but also have reported the presence of phosphorus and nitrogen in the compound The nutritional significance of cobalt phosphorus and iron for animals and human beings will have to be re evaluated when the biochemical significance of vitamin B_{12} is better understood

Vitamin B_{12} is rather widely distributed in relatively high amounts in cow manure fish meal, pancreatin papain eggs whey milk powder beef extract and the cultures of a number of microorganisms The

co workers in Switzerland and Dakin, Ungley and West working in the United States and in Great Britain all produced high concentrations of this material

About three years ago it was shown that both folic acid and thymine are effective in producing blood regeneration in patients with certain macrocytic anemias in relapse [2] and it also was shown that they neither prevent nor control the symptoms arising from the degeneration of the posterior and lateral columns of the spinal cord [3] Since neither of these substances was found in great concentration in most of the liver extracts the search for the active principle in liver continued unabated

All attempts to isolate the crystalline material were hindered by lack of a reliable assay method In 1947 Shorb [4] found in liver extracts a growth factor required by *Lactobacillus lactis Dorner* in concentration bearing a linear relationship to the potency of the extracts used in the treatment of pernicious anemia Rickes Brink, Koniuszy Wood and Folkers aided by this assay method isolated small amounts of a red crystalline compound which was highly active for the growth of the *Lactobacillus lactis Dorner* and also was highly active in initiating a positive hemopoietic response in persons with pernicious anemia They suggested the name vitamin B_{12} since the biological role of the new compound was so little understood and since this name had only nutritional significance and connotation

Smith [6] in Britain isolated the same type of crystals from liver eight days after the Merck publication He and his associates used the recently introduced method of partition chromatography to prepare substances containing approximately 3 per cent of the active principle Then by treatment with trypsin followed by more chromatography they produced tremendous concentration with the final crystallization from aqueous acetone

Biochemistry and Physiology

Vitamin B_{12} is a red crystalline compound which has not been prepared synthetically Microphotographs of this vitamin can be seen in Fig 67 When heated on the micro stage the crystals lose their red color at about 212° C and do not melt below 300° C

The structural formula of vitamin B_{12} is not known Intensive and excellent studies are being made independently by Folkers and the Merck Research Laboratories group and by the British investigator E Lester Smith [8] and his associates in the Glaxo Laboratories Emission

The onset is characteristically insidious The initial complaints are fatigability weakness numbness tingling stiffness headache nausea lack of appetite vomiting dizziness shortness of breath palpitation diarrhea pallor abdominal pain and glossitis By the time the anemia is severe the skin and sclerae often are lemon yellow in color By this time complaints referable to the nervous system are present These complaints may be associated with mental disturbances peripheral neuritis or spinal cord degeneration Macrocytosis is characteristic of the blood in persons with pernicious anemia and during the relapse stage the bone marrow is hyperplastic Failure to secrete free hydrochloric acid in gastric juice after histamine stimulation is most characteristic of persons with this disease

Diagnosis

A clinician can easily diagnose the average case of pernicious anemia in relapse Glossitis numbness and tingling of the extremities weakness macrocytic anemia hyperplastic bone marrow with megaloblastic arrest and achlorhydria form a clinical picture which is extremely well known Atypical cases even in relapse are difficult to diagnose and experts may disagree in their interpretations of the findings The most competent physician cannot make a positive diagnosis when the patient is in full remission irrespective of how thoroughly the physical examination and laboratory studies are made

Prevention and Treatment

At the present time there is no known method of preventing pernicious anemia Since it cannot be prevented replacement therapy is essential The hemopoietic response of patients in relapse with pernicious anemia, nutritional macrocytic anemia and tropical sprue to vitamin B_1 is shown in Figs 2 3 and 4 respectively

Vitamin B_1 is effective in promoting regeneration of the red blood cells hemoglobin white blood cells and platelets in properly selected patients but we do not have sufficient studies to recommend the average dose required either for full regeneration or for maintenance As little as 1 microgram will produce a detectable blood response in an occasional case whereas as much as 5 micrograms may fail to produce

natural vitamin then may be said to occur in a number of plant animal and microbiological materials yet it does not occur in abundance Apparently man cannot synthesize the material, although the micro organisms in his alimentary tract may do so, nor can he store it to any great degree in his tissues

Pathological Physiology

Vitamin B_{12} or substances acting similarly are required in minute amounts to maintain most if not all forms of life It is necessary for the growth of certain microorganisms It stimulates the growth of secondary-generation rats weaned from mothers that were maintained during gestation and lactation on a diet devoid of animal protein It counteracts the growth retarding effect of thyroid extract when fed to immature rats, and it has been found to have "animal protein factor" activity in chicks obtained from hens fed all-vegetable-protein rations Thus, there is a possibility that vitamin B_{12} is identical with, or closely related to, the animal protein factor recovered from cow manure and from a number of microorganisms[2, 9, 280]

When patients with Addisonian pernicious anemia in relapse are given vitamin B_{12}, it produces a positive hematologic response[31] and benefits strikingly the patient who has acute glossitis and acute combined degeneration of the spinal cord It has been found to be effective in producing a hemopoietic response and great symptomatic improvement in persons with nutritional macrocytic anemia tropical sprue and non tropical sprue[28, 83, 84, 28, 286, 287] When it is realized that this material can be given in microgram quantities and produce regeneration of a number of litres of blood and be followed by a great increase in appetite and body weight it must be thought of as something affecting one of the profoundly important enzyme systems of the body

Symptomatology

Vitamin B_{12} has been isolated so recently and exists in the pure state in such minimal quantities that vitamin B_{12} deficiency has not been described as such The authors are of the opinion that pernicious anemia can be considered the result of vitamin B_{12} deficiency Pernicious anemia is too well known to repeat a description of it here in detail

offers the physician a known dose of a pure compound and should thus minimize the variation in therapeutic response

Potent doses of the new vitamin may be given without physical discomfort to the patient. A number of persons with pernicious anemia develop allergy to liver extracts and in some parts of the world the

HEMOPOIETIC RESPONSE OF A PATIENT (T.L.) WITH NUTRITIONAL MACROCYTIC ANEMIA TO VITAMIN B_{12}

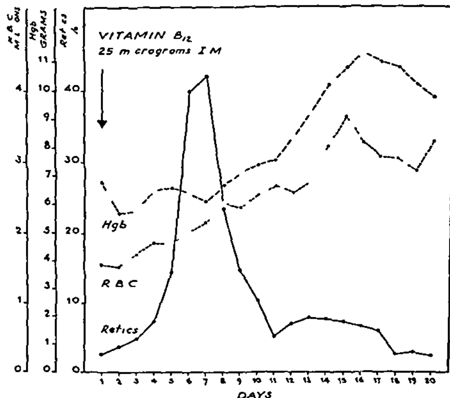


Fig. 3

commercial liver extract preparations are not potent. Persons who have acute manifestations of subacute combined degeneration of the spinal cord are benefited when given vitamin B_{12}.

Suffice it to say that the limitations and therapeutic indications of vitamin B_{12} are not yet fully known but it is by far the most potent

a response in a case that will respond well following the administration of 10 micrograms The individual variation in the amount required can be overcome however by giving increased dosage We have seen no case that did not respond somewhat to 25 microgram amounts and we have seen no case that did not regenerate several million red blood cells when as much as 100 micrograms was injected

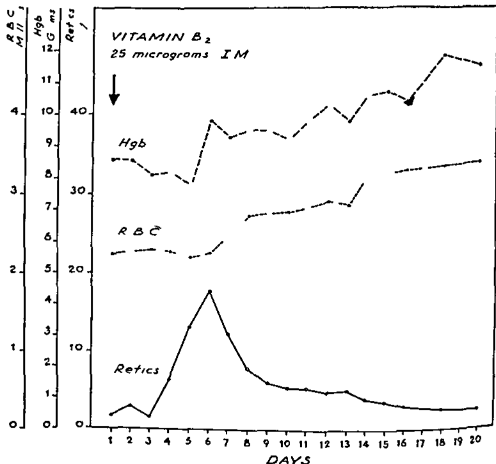


Fig 2

We have not had sufficient material to study properly oral therapy and cannot make any comment about it at this time The clinical possibilities of vitamin B_{12} then are not altogether predictable although it

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therapeutic agent per unit of weight yet introduced into medicine Unfortunately it is still in the experimental stage, and the supplies of vitamin B_{12} are inadequate as yet for routine treatment of pernicious anemia

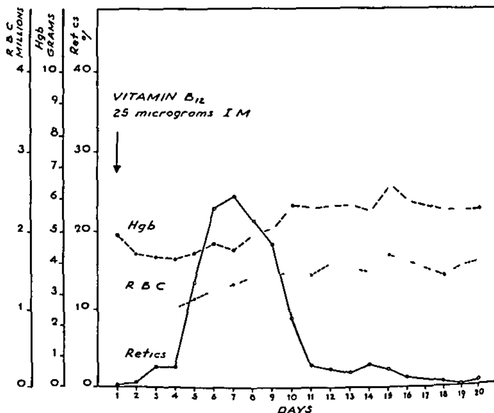


Fig 4

Toxicity

The practicing physician should keep in mind there is such a great difference between the therapeutic dose and any theoretical toxicity of vitamin B_{12} that there is no danger of even accumulative toxicity and he should remember that it is a safe and effective therapeutic agent when it becomes available in sufficient amounts to use in practice

CHAPTER XI

CLIMATE IN HEALTH AND DISEASE

BY CLARENCE A. MILLS

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INTRODUCTION

Climate as a factor in the health of man is now beginning to receive

484 SPIES T D STONE R E GARCIA LOPEZ G MILANES F ARAMBURU T and LOPEZ TOCA R The association between gastric achlorhydria and subacute combined degeneration of the spinal cord Postgraduate Medicine 1948 IV 89

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are frequent and abrupt but much more evidence must be accumulated before the physiology of their effects can be understood clearly Physicians should realize that individuals differ greatly in their sensitiveness to storm changes Some are utterly unfitted for existence in a stormy region and should be advised of the advantages of migration to a region of less turbulence

This chapter is offered in the hope that it may help physicians to a clearer understanding of the workings of these climatic factors Knowledge in this field still is in the stage of rapid expansion but sufficient definite information already is at hand to warrant positive advice along several lines Such advice will be presented in the final pages of the chapter after the mechanism and details of climatic effects have been discussed The newness of much of this field of knowledge necessitates for its clear understanding a rather comprehensive presentation of the physiological principles involved

Physiological Considerations of Climatic Effects

Human Energetics

Since the most fundamental effects of climate are exerted upon the energetics of human existence let us first consider the body as an energy conversion machine At all times it lives and functions only by virtue of the cellular combustion of foodstuffs Much of this combustion energy is wasted however because of low working efficiency Man himself has designed a machine of greater working efficiency than is the human body As high as 37 per cent efficiency has been reached in Diesel engines while even gasoline motors may reach the 20 to 25 per cent efficiency exhibited by man (1) the horse (2) and the dog (3) The human body however is much more limited than are inanimate motors in the temperature range within which it can function well Even a very few degrees of rise or fall from the normal body temperature level seriously interferes with efficient functioning

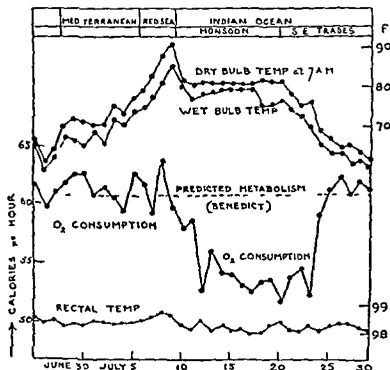
To meet this handicap the body has developed an intricate mechanism for control of rate of heat loss Through the vasomotor control of blood supply to the skin the amount of heat reaching the body surface for heat dissipation can be altered with great rapidity Normal heat loss from the deeper tissues by direct conduction is slow and is impeded by the insulating layers of fat encountered but the blood with its high specific heat capacity and rapid circulation can carry internal heat to the body surface at a rapid rate Blood flow through skin capillaries may be increased as

the attention its importance warrants Through its dominance of ease of body heat loss it largely determines the energy level upon which man may exist in a given region and we now know that much more than mere working ability is attached to this energy level of existence All vital functions of the body are based upon the energy derived from cellular combustion of foodstuffs but as an energy conversion machine the body is not of high efficiency It is thus very sensitive to the ease with which its waste heat can be thrown off and it is here that climatic dominance is exercised Where heat loss is accomplished easily growth is most rapid maturity comes early resistance to infection is highest energy for thought and action is most plentiful and health assumes a more positive and dynamic quality As heat loss becomes more difficult all these indices of vitality are depressed and a lower more vegetative level of existence results

Particularly in America with its intense climatic contrasts should there be among physicians a clear understanding of these forces at work Enlightened medical practice now goes far beyond the mere diagnosis and treatment of disease Underlying most research into the treatment of disease has lain the ideal of disease prevention the maintenance of unhindered health Among the factors influencing this maintenance of health climatic environment probably will be found to be equally as important as adequate food supply or genetic background Proper food i of course an essential requirement but so too is the ability to utilize this food With the lower combustion level of people in tropical warmth more vitamins are needed to utilize each gram of food than are required for optimal response in cooler climates Man is less energetic in warm climates but he is a more efficient working machine and shows less evidence of wear and tear In cooler regions where more dynamic and buoyant health prevails the most acute and worrisome problems facing the medical profession arise from the wear and tear of too stressful an existence

While mean temperature level and ease of body heat loss thus dominates the energetics of life there is a second climatic factor which in some regions seriously disturbs the smooth flow of healthful functioning Storminess or atmospheric turbulence with the accompanying sudden changes in temperature pressure humidity etc is now recognized as a major disturbing factor in certain regions of the earth where cyclonic storms prevail These sudden changes in the atmosphere seriously disrupt tissue functioning in ways as yet little understood and seem closely related to the initiation of many types of acute infectious attacks Storm changes certainly constitute a major health factor in regions where they

forced by difficulty in heat loss necessarily must mean a curtailment of energy available for carrying out such vital functions as growth work performance tissue repair and the fight against infectious invasions Such direct linking of these vital functions to tissue combustion rate and ease of body heat loss although logical enough has not received the appreciation its importance warrants Indeed there has existed among medical men in America a disbelief that any such dependence really exists This disbelief dates back to the publication of a paper by Benedict and



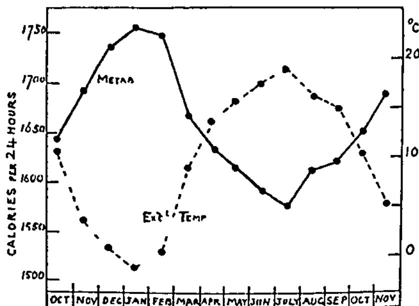
Daily observation of basal metabolism of C J M during a voyage from London to Australia June–July 19 3 and daily record of the temperatures of the dry and wet bulb thermometers at 7 A M

FIG 2 Fall in oxygen consumption in tropical heat

Cathcart[1] in which they cite oxygen consumption data on 14 subjects in Boston and claim a lack of any seasonal influence Even though their own data presented in their article do show a strong tendency for lowest consumption rate to occur in July or August and this in Boston where summer heat is rarely severe this article has been extensively quoted

much as 30 fold within a few minutes when a sudden need arises When this increased blood flow through the skin proves inadequate for quick elimination of the heat of combustion then the sweat glands become active and make possible a still greater increase in rate of heat loss by water vaporization

This intricate heat control mechanism functions quickly to meet sudden changes in heat production as in bodily activity or in the ease of



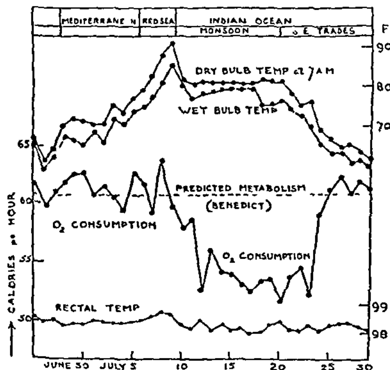
Mean monthly metabolism and mean monthly temperature Gessler (1925) observations on himself

Fig 1 Seasonal variations in oxygen consumption

heat loss as in sudden external temperature changes However with more prolonged changes in the ease or difficulty of heat loss the body adapts by an increase or decrease in its basic rate of tissue combustion Thus external heat that lasts only a few days calls into play only the vasomotor and sweating mechanisms but if such heat persists for 10 days to 2 weeks then there occurs a marked suppression in tissue combustion rate Therein lies the chief reason why severe summer heat waves may persist for weeks but cause frequent prostration and death in the affected population only during the first 10 days or so

It is this combustion rate response to the more prolonged changes in external temperature level and ease of body heat loss that holds greatest significance for man Any decrease in total tissue combustion level en

forced by difficulty in heat loss necessarily must mean a curtailment of energy available for carrying out such vital functions as growth work performance tissue repair and the fight against infectious invasions Such direct linking of these vital functions to tissue combustion rate and ease of body heat loss although logical enough has not received the appreciation its importance warrants Indeed there has existed among medical men in America a disbelief that any such dependence really exists This disbelief dates back to the publication of a paper by Benedict and



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since as indicating that tissue combustion rates are independent of external temperature levels

This point is of such basic importance in any analysis of climatic effects that recently it was made the subject of a special article[5] in which the available evidence was presented and discussed As set forth in that article the evidence points conclusively to a clear inverse relationship between tissue combustion rates and prevailing external temperature levels in both men and animals Fig 1 shows this relationship as found by Gessler[6] through all seasons of a year at Heidelberg Germany Fig 2 indicates the marked suppression in resting oxygen consumption rate

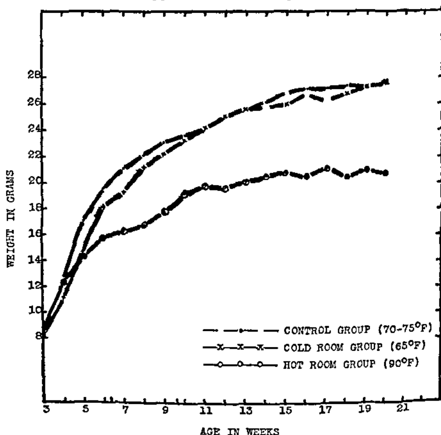


FIG 3 Growth of white mice at different temperatures

found by Martin[7] in himself during his passage through the zone of tropical heat on a trip from London to Melbourne Practically all investigators who have looked for this heat suppression of combustion rate have found it Let us next see what it means in terms of growth and other vital functions

Growth Rates at Different Temperature Levels

All types of experimental animals suffer a growth retardation when heat loss becomes difficult Fig 3 shows the extent of this growth suppression in white mice kept at 65° F 72° F and 91 F This happens even though all factors of existence other than ease of heat loss are kept constant Animals at 91° F eat only about half as much food as at

FOOD CONSUMPTION & RAT GROWTH RATES
AT DIFFERENT TEMPERATURE LEVELS

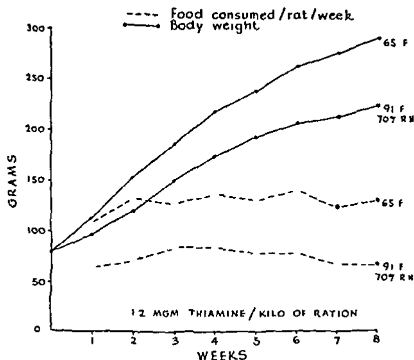


FIG 4 Food consumption and growth rate in heat and cold

65° F In Fig 4 is shown this difference in food consumption by young Wistar rats and its direct relationship to their rate of growth and final adult size Herein lies the principal reason why domestic animals do so poorly in tropical warmth giving lean stringy meat of strong flavor Coarseness of the tropical forage crops and leaching of soils under the heavy rainfall may be factors of considerable weight but suppression of

tissue combustion rate by difficulty in body heat loss probably is more important

Children show this same retarded growth rate and inferior adult size under tropical heat conditions while in the optimal coolness of middle temperate regions growth is most lusty and adult stature greatest[8] The close relation of such growth differences to oxygen utilization is emphasized by the marked differences in vital lung capacity exhibited by individuals from the two types of climate Vital capacity in Filipino college students is only a little over half as great as that of students in northern United States

Back through human history man s stature and development has fluctuated with slow changes in earth temperatures Middle Age warmth saw a marked decline from early Greek levels in the size of man and in his speed of development while with the colder centuries since the time of the Renaissance the race has again shown a striking rise from the low Middle Age standards The menarche in girls of early Greece came at 13 years of age according to Hippocrates but with the retarded development of the Middle Ages the menses did not begin until the 16th 17th and 18th years in European girls A marked quickening in development has been in evidence during the last few centuries of lower world temperatures with the menses now coming 1½ years earlier than they did even 4 decades ago and the adult male height being now four inches greater than in Revolutionary days Man was really runt like through the warm centuries of the Middle Ages small of stature and fine boned The knights who wore the suits of armor now on display in museums although probably the best physical specimens of the day must have been far below the standards of today for a well developed American boy of 14 years would have great difficulty getting into any of the suits now on display in the Tower of London

World temperatures have been rising quite generally again in recent decades and the long period of improvement in racial physique seem perhaps about at an end College youth in America where nutritional standards have never been higher are now showing signs of a reversal in the growth tide The menses are now tending to begin later and the stature to be slightly less with each year s entering class of freshmen in schools of lower and middle temperate latitudes although improvement still proceeds apace in schools of higher latitudes where depressive summer heat has not yet reached effective levels The human race does then seem to respond to slow changes in earth temperature levels in the same manner that experimental animals respond to artificial changes in ease of body heat loss This fact is of fundamental importance in racial welfare

for it perhaps accounts in large part for the slow undulations of advance and recession which the race has undergone through past ages and may some day give a clue to our course through the coming decades and centuries when we shall have become able to predict future temperature trends The matter is not just one of recession in rate of growth and development but involves also all the other factors of life dependent upon the dynamics of cellular combustion Ability and urge to accomplish along both physical and mental lines and the positiveness of health itself seem closely bound up in this temperature dominance over human dynamics

Development of Sexual Functions

Onset of sexual functions and degree of fertility are closely linked to ease of body heat loss and tissue combustion level Most rapid development and highest fertility occur at environmental temperatures around 65° F As difficulty in heat loss comes on and growth rate slackens we regularly see also a later onset of sexual cycles in young females both human and animal and a lowered fertility[9] Animals mate freely at 90° F but conceptions are difficult to obtain and result in small litters of puny young while at 65° F almost every mating results in a large litter of lusty offspring Histological changes in gonadal tissues indicate that this suppression of reproductive tissue is extensive and very real Spermatogenic activity in the testes is almost obliterated within 10 to 14 days of application of tropical moist heat After several weeks of adaptation some recovery of function occurs but to a much lower level of activity than is seen at lower temperature levels

Man living under natural climatic habitats shows just as striking sexual variations at different levels of environmental temperature as do laboratory animals Onset of the menses in girls occurs earliest in middle temperate latitudes and comes at a progressively later age as more and more severe tropical heat is encountered At the present time here in North America earliest menarche is found in the upper half of the Mississippi basin Nowhere else on earth do children grow with such lusty vigor and enter such early adolescence Development in the Gulf States is somewhat retarded by the long summer of tropical moist heat but most severe suppression takes place in the tropical lowlands where depressive moist heat renders heat loss difficult at all times

Medical literature and lay belief back through the centuries at least to the time of Hippocrates has held that earliest onset of the menses occurred in the tropics Even though all recorded statistics contradicted

this belief still it is encountered among people of all lands both lay and medical Since we know it has been handed down through medical literature for two thousand years without factual support, we can well presume that it may have originated several thousand years earlier still Only 20 000 or so years ago present middle temperate regions had polar climates and optimal temperature conditions for man were to be found only in what are now tropical or subtropical lands That such beliefs perhaps once based upon real facts can be handed down through many thousands of years without further supporting factual background is well illustrated by the ancient astrological beliefs so widely held today even among intelligent people

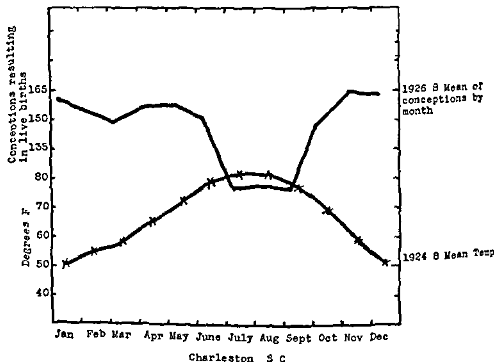


FIG 5 Variations in conceptions Charleston S C

Fig 5 illustrates the sharp suppression of human fertility that comes with difficulty in heat loss Wherever human populations are exposed to seasonal swings in mean monthly temperature highest conception rates nearly always occur when the mean temperature level is near 65° F As mean temperatures rise above 70° F or fall below 40° F fertility is reduced With really severe moist warmth as in Japan s monsoon summer heat or in the prolonged severe heat waves of the upper Mississippi valley

in North America conceptions may be reduced as much as 50 per cent Nor is this reduction in conceptions merely a result of less frequent intercourse in hot weather for there occurs no significant reduction in the frequenting of houses of prostitution Apparently both men and animals continue the mating urge in hot weather but suffer a sharp drop in biological fertility

There has been much written about child mothers among tropical peoples but it is really among populations of middle temperate regions that fertility has its earliest onset Later marriage ages of the more highly industrialized nations of the temperate zones tend to mask the early onset of fertility but it has been brought out by a study of illegitimate first births[10] At Cincinnati Ohio the average maternal age at illegitimate first birth was found to be 18 1 years and at Richmond Virginia 18 2 years for negro girls while at Panama it was 19 3 years and in the Philippines 21 8 years The average lag from menarche to first conception with these illegitimate first births was 3 9 years at Cincinnati 4 0 at Richmond 4 5 at Panama and 6 3 in Manila This markedly later age at first conception in the tropics occurs even in the face of a much greater promiscuity of premarital intercourse and lessened likelihood of chances for effective impregnation being missed Maternal age at the first child birth in Manila is the same regardless as to whether the mother be married or single

Malnutrition from any cause tends to retard development of the sexual functions Difficulty in body heat loss is no more effective in this respect than is inadequacy of available food supply either in total amount or in composition or serious childhood illnesses The menarche usually is delayed in girls who have been subjected to any of these depressing influences through their childhood years

Resistance to Infection

Although such factors as malnutrition vitamin deficiency and exhaustion usually have been considered important in determining the body s ability to fight infection there has been little apparent inclination to relate this ability to tissue combustion level Yet such a relationship would seem logical since all vitality factors must have their functional basis in the energy liberated from such combustion It is infectious disease which kills people living under depressing tropical warmth while the more energetic residents of middle temperate regions die mainly from the degenerative and breakdown ailments In 1932 we showed that ability to survive tuberculous infection was markedly higher in Cincinnati

residents who were born in the North than in those born in the Gulf States[11] Dealing only with tuberculosis deaths among the indigent population of Cincinnati it was shown that the survival time from first symptom to death was almost twice as long in patients born in northern United States or North Central Europe than it was in those born in the Gulf States of North America or in the Mediterranean countries of Europe Ability to survive acute appendicitis attacks also is markedly higher in the North than in the South[1] These facts will be discussed more fully on a subsequent page

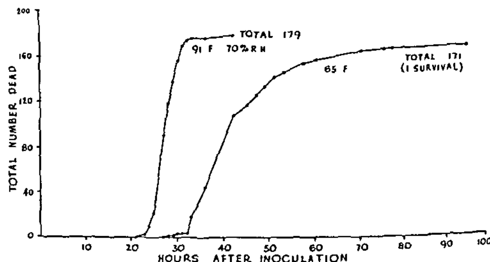


FIG 6 Resistance to infection in heat and cold

Human disease statistics however are influenced by too many extraneous factors to be of any great value in determining climatic effects unless they can be substantiated by studies on experimental animals under carefully controlled conditions Human data may supply indications of existing differences or trends but conclusive proof in such a matter must come from laboratory studies Fortunately such studies have now shown that ability to fight infection is definitely higher under conditions that facilitate body heat loss than it is where heat loss is difficult With all other existence factors except ease of body heat loss held constant practically all mice adapted to 90° F will be dead after inoculation with a given dose of pneumococci organisms before those adapted to 65° F even begin to succumb Fig 6 presents this fact in striking fashion and if one uses a less lethal organism such as a hemolytic strepto-

coccus then the minimum lethal dose for the 65° F mice is found to be about four times as great as it is for those kept at 90° F. Antibody production after typhoid vaccine injection into rabbits is almost twice as great in those animals kept at the lower temperature.

Locke[13] has provided support also for the idea that combustion level is an important factor in determining resistance to infection. He found that ability of animals to survive pneumococcic inoculations or of human beings to maintain freedom from respiratory infection was related directly to their rate of oxygen utilization. The matter needs more thorough study, but in the main it would seem that man's susceptibility to infection and his chances for survival are conditioned rather markedly by his ease of body heat loss and the resulting tissue combustion level allowed him. Temperate zone man does not then enjoy greatest freedom from respiratory disease during the summer months because of better tissue vitality as has been so commonly supposed. Actually the fatality rate per 100 cases of acute appendicitis is almost twice as high in summer heat as in northern winter cold, and tuberculosis runs its most rapid course when symptoms of disease activity first appear in summer heat. It would now seem almost certain that the summer freedom from respiratory infection is attributable in very large part to the lessened storminess of that season and the greater freedom from body chilling. More will be said about this subject on a later page.

Vitamin and Protein Requirements

Since human vitality and energy level seem so dependent upon ease of body heat loss and tissue combustion rate, it is well to look into the combustion process itself. Perhaps tissue requirements for the combustion catalysts are higher when the combustion rate is slowed down by difficulty in heat loss. With the lowered food intake of hot climates or in summer heat it may well be that a higher dietary content of thiamine and of other combustion catalysts of the vitamin B group is needed to maintain optimal concentration for proper tissue oxidative processes. It has quite generally been considered, largely as a result of Cowgill's studies[14], that thiamine requirement is determined by the amount of glucose there is to be burned, that a more or less constant ratio exists between thiamine requirement and total non-fat calories of the diet. His studies, however, and those of others in this field were carried out at approximately optimal environmental temperatures for the animal subjects, so that there was no way of knowing whether this ratio might not vary as external temperatures were raised or lowered.

In more recent studies on this point[15] it has in fact been found that the optimal requirement for dietary thiamine is twice as high at 91° F than it is at 65° F Animals show definite inadequacy in the heat at dietary thiamine levels twice as high as those at which inadequacy ap-

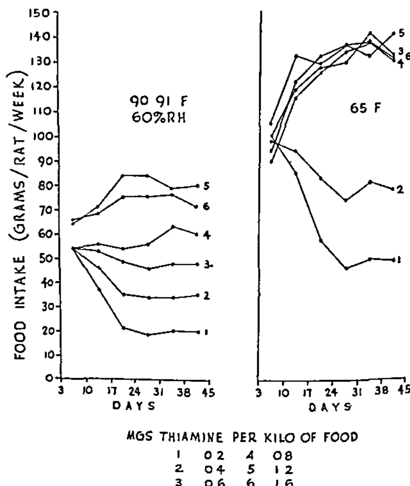


FIG 7 Dietary thiamine and food consumption in heat and cold

pears in a cool environment Studies in progress indicate that somewhat similar findings will be obtained for others of the vitamin B fractions pantothenic acid deficiency already having been found to develop with much greater rapidity at 91° F than at 65° F

Fig 7 shows clearly the marked difference in optimal dietary thiamine level for Wistar rats kept in moist warmth and in a cool environ

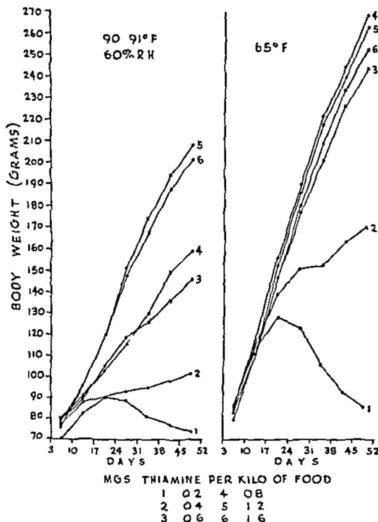


Fig 8 Dietary thiamin and growth rates in heat and cold

ment At 91 F food consumption is greatest in those animals using a diet containing 1 2 milligrams of thiamine per kilo while at lower levels

of dietary thiamine there is almost a quantitative relationship between food consumption and thiamine content. At 65° F. on the other hand food consumption is sub-optimal only at the two lowest thiamine levels 0.2 and 0.4 milligrams per kilo of food.

In Fig. 8 these differences in dietary thiamine requirements are brought out even more quantitatively by differences in rate of growth. At 65° F growth is almost optimal with all the groups receiving 0.6 milligrams or more per kilo of food, although the 0.8 milligram group was found to do best and usually to show the greatest gain in weight per gram of food eaten. With rats kept at 91° F best growth was obtained at the 1.2 milligram level but with little difference at 1.6 milligrams. Best growth efficiency (grams gain in weight / grams of food eaten) was found most often at the 1.6 milligram thiamine level in the heat (90–91° F) but at 0.8 milligrams in the cold (65° F.) as shown in the curves in Fig. 8.

These *food consumption and growth differences at varying thiamine* intake levels persist on through to adult life, giving at the lower thiamine levels the scrawny, stunted specimens so similar to those commonly seen among human populations living under tropical lowland heat. Many students of nutritional problems have held that a higher protein intake, particularly of animal proteins, would greatly improve the nutritional state of tropical people.

Higher cost of such protein foods has prevented any widespread trial of this idea, but unpublished results from the author's laboratory have *given indications that such a step would not be beneficial in tropical* heat even if it were economically feasible.

Fig. 9 illustrates in striking fashion the handicap placed upon animals living at 91° F. when their dietary protein is increased only moderately. The added difficulties in heat dissipation that result from the increased dietary protein with its higher specific dynamic action seem just as depressive to growth as do still higher external temperatures.

It is unfortunate indeed that the greater part of our dietary supply of vitamin B fractions *comes in foods which are rich in protein*: meats, milk products, nuts, legumes. Cereal grains provide the only exceptions and with the two most widely used, wheat and rice, the vitamin stores are largely removed in milling processes. Tropical natives thus are doubly handicapped. Their need for vitamins of the respiratory catalyst type is sharply higher than in cooler lands, while the principal foods through which they might meet this higher need are more expensive and intensify their problem of difficulty in body heat loss. Fruits and starchy tubers

which supply such a large part of the tropical dietaries are low in vitamin B fractions but can be utilized by tropical natives with least intensification of their heat loss difficulties

Man's higher requirement for the vitamin B fractions in tropical warmth probably plays an important part in the widespread occurrence there of such deficiency states as beri beri and pellagra The subject needs a thorough investigation for upon this situation may hinge a considerable part of the malnutrition and low physical level seen among tropical populations The magnitude of the problem can be appreciated only when it is remembered that half of the earth's human population

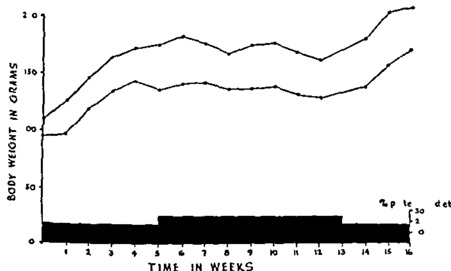


FIG 9 Protein intolerance at high temperature

lives under just such depressive heat as is being discussed here We can as yet only guess at the many bearings this variation in vitamin requirement at different temperature levels may have in the problems of human welfare Since it affects directly cellular combustion and the source of energy for all body functions it must of necessity have important bearings on all the vital processes and functions of the body A whole new field seems to be opened up by this dynamic view of physiological response to climate

Climate and Disease

The preceding discussion of climatic physiology provides a most useful background for an understanding of the geography of many diseases Tropical people with their more sluggish combustion rate and lowered vitality die largely from the infectious diseases energetic residents of cooler lands die more from the breakdown and degenerative diseases Only with pneumococcic and streptococcic infections largely respiratory or of the nasopharynx, is the attack frequency higher in temperate regions and then only during the seasons of great cyclonic storminess Since these disease differences are based largely upon demonstrable differences in physiological response to living environment and are susceptible to a considerable degree of control it seems wise that the medical profession consider them against their proper physiological background

It is not at all surprising that clearest climatic relationships should be found for the diseases of metabolic over stimulation or breakdown Metabolic stress rises highest in middle temperate regions where most nearly optimal heat loss conditions prevail while toward tropical warmth evidences of such stress progressively decrease Diabetes with its breakdown in ability to metabolize the glucose upon the combustion of which depends all bodily energy shows this climatic relationship perhaps most clearly but the relationship is also quite evident for pernicious anemia with its exhaustion in the production of red cells to carry the oxygen from lungs to tissues Toxic goiter and hyperthyroidism seem likely to be involved in this same environmental influence Perhaps most worrisome to the medical profession of the stimulating regions are the growing evidences of stress and failure in the vascular system Upon this system falls the most direct load of any tissue combustion increase for it must transport to the tissues all the needed combustion factors The advance of sudden heart failure toward earlier and earlier ages in American men of middle temperate latitudes is presenting the medical profession with an acute health problem to consider Over two thirds of the American physicians dying in 1939 did so from primary failure of one sort or an other in the circulatory system Addison s disease with its adrenal failure and other exhaustion states such as myesthenia gravis and neurocirculatory asthenia also most frequently occur in these same middle temperate latitudes And for some reason as yet little understood it is in these same latitudes that cancer is presenting its greatest menace to man Leukemia which some consider to be a form of neoplasia is almost exclusively a cool climate disease

Infectious diseases present the other side of the picture for with them

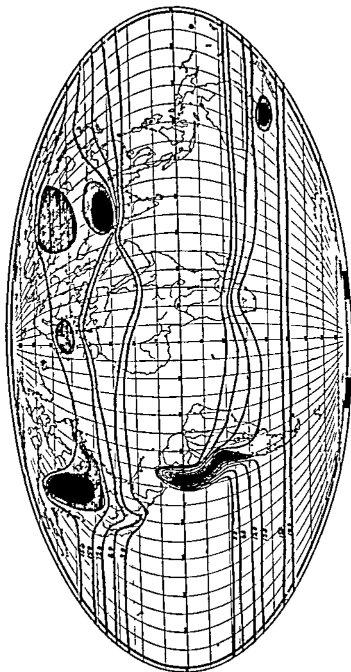


Fig 10 Climatic stimulation over the earth

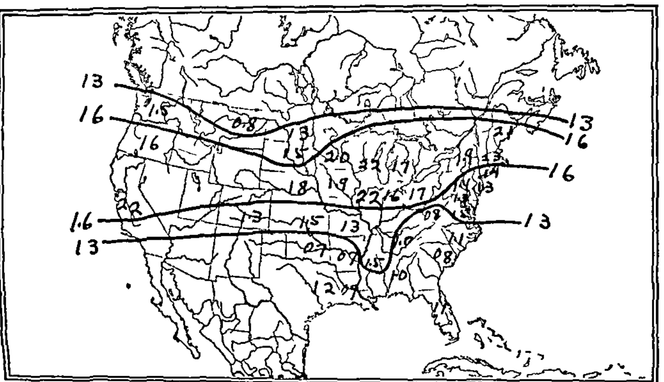


Fig 11 Diabetes deaths per 100 000 populat on Rural Wh te race o ly — annual a erage (1931-5)

greatest frequency and highest death rates go hand in hand with lowered tissue resistance in the debilitating warmth of tropical and subtropical regions. Temperatures there are more nearly optimal for parasitic and bacterial contamination of water and food supply, it is true, and added to this is the tremendous problem of insect vectors, but working beneath these major health threats in the tropics is the lowered general tissue vitality from sluggish cellular combustion. Fig. 10, showing regional differences in the intensity of climatic stimulation over the earth, is presented here so that the reader may have before him this rough idea of the metabolic driving force being exerted upon man in the different regions. The methods used in calculating the indices of climatic stimulation have been described in detail elsewhere[18]. Let us see in greater detail in succeeding paragraphs of this section just how important these effects of climate may be for man.

Diabetes Mellitus

With 80 per cent of the total cellular combustion being glucose burning it is not surprising that evidences of stress should appear in the body's machinery for handling glucose under conditions that bring a prolonged and sustained increase in tissue combustion rate. No one knows as yet just what factors immediately determine which members of a population mass shall suffer this break in glucose metabolism, but the evidence is convincing that the severity of diabetes as a disease is strongly influenced in some way by climatic stimulation. While the disease occurs in tropical people, it is so mild as rarely to need attention and seldom results in severe ketosis; mild dietary management usually is sufficient for complete control. In the cooler and more energizing middle temperate latitudes, on the other hand, diabetes becomes a much more violent metabolic disturbance, with ketosis a frequent and real threat to the patients' lives and with eternal and painstaking care the price to be paid for its control.

Fig. 11 shows the marked increase in recorded diabetes mortality among rural populations from the Gulf States northward in America and the decline on into Canada past middle temperate latitudes. Failure of the band of high mortality rates to continue across the upper Plains States probably is due to the younger average age of the populations of those states. The disease is now increasing in severity there as the population ages, with those states showing the most marked rise in mortality rate. In urban populations the age differences are not so great and in Fig. 12 it is seen that the band of highest urban diabetes mortality extends entirely across the continent.

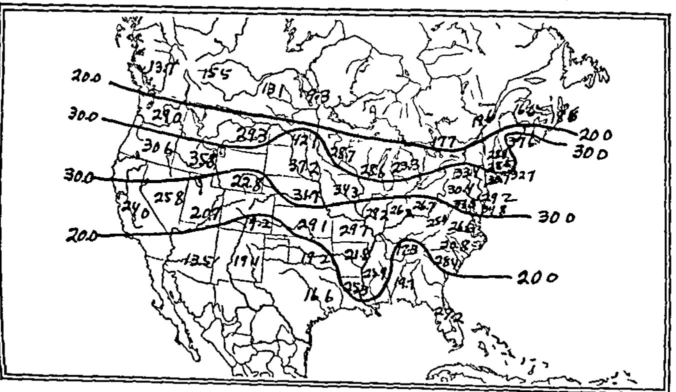


Fig. 1. Diabetes deaths per 100,000 population. Urban white race only — annual average (1931-5).

It is not yet clear just why evidences of climatic stimulation and metabolic stress should lessen on northward into polar cold much like they do toward subtropical warmth All metabolic and degenerative disease statistics do show a decline in severity northward from middle temperate latitudes and the onset of the menses in girls is progressively delayed the farther north one goes The reason may perhaps lie in the fact that in the milder winters of middle temperate regions people get outdoors more and really undergo greater exposure to increased heat loss than do people living through the prolonged winter cold of more northerly regions Whatever the explanation may be it does seem a fact that human vitality rises highest in middle temperate latitudes both north and south of the equator The moderating influence of the Gulf Stream on northwestern Europe seems to cause highest vitality there to appear about 15 degrees farther north than in America Britain northern France Belgium the Netherlands Denmark Germany and the southern parts of Scandinavia seem to form the European counterpart of the northern half of the United States in the matter of climatic stimulation

Fig 13 showing the ten fold increase in the negro diabetes death rate from south to north within the United States gives clear indication of the price this tropical race pays for its higher energy level on migration into the stimulation of cooler regions Vascular sclerosis in the negro is also a much more malignant disease in the northern states than it is in the south occurring with greater frequency and running a more rapid course Toxic goiter also becomes much more frequent and pernicious anemia makes its appearance in a race apparently free of the disease in warmer regions

Fig 14 shows the European center of high diabetes mortality to cover the same west central European countries shown in Fig 10 to be receiving the highest degree of climatic stimulation available on that continent Statistics for either total or urban death rates show diabetes in this area to be more severe than in other parts of the continent In South America the disease becomes a health problem only in the temperate coolness of Argentina and Chile while in Australia it is of low severity in the north and increases progressively toward the south

Diabetes specialists studying and handling the disease only in the regions where it is most frequent and severe are inclined to doubt these statistical indications of climatic or regional differences in the disease Less accurate diagnosis and reporting of causes of death they feel may account for most of the differences in mortality Extensive surveys of the disease in the living populations of Massachusetts and Arizona summarized in a recent paper entitled The Universality of Diabetes [17] was

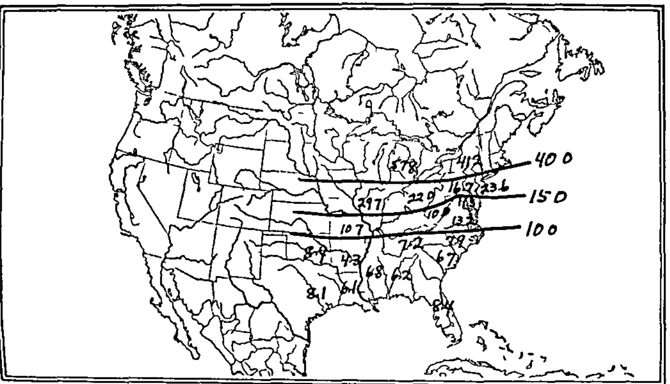


Fig. 13 Diabetes deaths per 100 000 population Rural colored race only — annual average (1931–5)

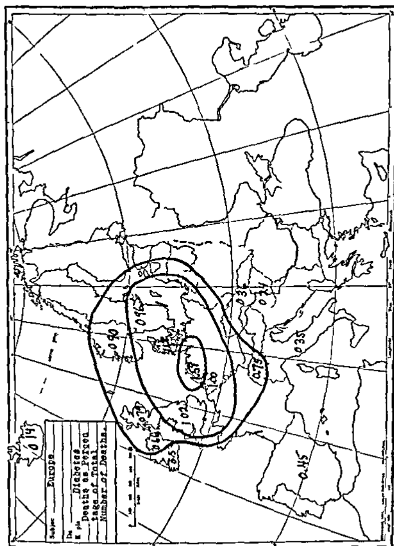


FIG 14 Diabetes death rates in Europe

claimed to contradict the idea that real differences do exist with such wide climatic variation as these two states show It is unfortunate that the southern state chosen for comparison with Massachusetts should have been one so heavily populated by former migrants from northern regions probably standing next to Florida and California in this respect But even with this high proportion of migrants from the north the survey indicated a considerably lower diabetes death rate per 1 000 cases in Arizona than was found in Massachusetts

The evidence for climatic differences in diabetes is being discussed in considerable detail because this disease has been studied more thoroughly than have the other metabolic disturbances and because it bears such a direct relationship to tissue combustion rate and metabolic stress Then too the milder course followed by the disease in warm climates is a point of great therapeutic importance for the people who must live out their remaining life span under its handicaps

Pernicious Anemia Toxic Goiter and Addison s Disease

Pernicious anemia shows just as clear evidences of climatic variation in severity as does diabetes It forms a real health problem only in those same stimulating temperate regions where diabetes is so severe and is seen rarely in tropical warmth The same holds true for *toxic goiter* and *Addison s disease* Higher death rates from these metabolic diseases in middle temperate regions cannot be due only to the reduced infectious disease death rates there prevailing for there is more frequent metabolic breakdown at every age throughout life Death rates for these diseases are about twice as high for every age group in northern United States as for comparable populations along the Gulf of Mexico A similar relationship seems to hold for other continents of the earth although lack of uniformity in mortality records makes difficult so clear a presentation of the differences as is possible in America

Arteriosclerosis and Heart Failure

Arteriosclerosis and *heart failure* statistics are in general still too confused and lacking in uniformity of nomenclature and diagnostic criteria to be of much value There seems little doubt that diseases of the heart and vascular system constitute a far more serious health problem in temperate regions than in tropical warmth The differences seem to be of about the same order as with the metabolic diseases This would be quite in line with expectation if circulatory failure is dependent upon stress for

the primary work load of a higher tissue combustion rate falls upon the circulatory system as the oxygen carrier. Although general mortality statistics are unsatisfactory to bring out this relationship, recently it has been demonstrated in another way[18]. Fig. 15 shows the clear inverse relationship of non-infectious heart failures to mean monthly temperature

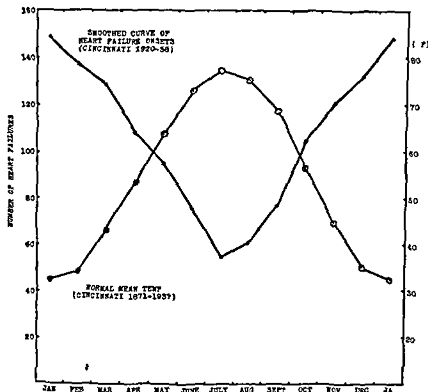


FIG. 15. Heart failure frequency and mean temperature level

level throughout the year at Cincinnati, using only fever-free heart failure admissions to the Cincinnati General Hospital over a 20-year period. Such heart failures not only show this striking seasonal variation in frequency, but they fluctuate also with the severity of the winter cold. During certain warmer Cincinnati winters admission rates for such heart failures were only a quarter as high as during winters of normal cold. Rheumatic and arteriosclerotic types of heart failure show this relation to prevailing external temperatures, but not those due to syphilis.

Vascular sclerosis in old age might be expected in any region, but it seems that only in the more energizing regions of the earth do its devas-

claimed to contradict the idea that real differences do exist with such wide climatic variation as these two states show. It is unfortunate that the southern state chosen for comparison with Massachusetts should have been one so heavily populated by former migrants from northern regions, probably standing next to Florida and California in this respect. But even with this high proportion of migrants from the north the survey indicated a considerably lower diabetes death rate per 1,000 cases in Arizona than was found in Massachusetts.

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Pernicious Anemia, Toxic Goiter and Addison's Disease

Pernicious anemia shows just as clear evidences of climatic variation in severity as does diabetes. It forms a real health problem only in those same stimulating temperate regions where diabetes is so severe and is seen rarely in tropical warmth. The same holds true for *toxic goiter* and *Addison's disease*. Higher death rates from these metabolic diseases in middle temperate regions cannot be due only to the reduced infectious disease death rates there prevailing, for there is more frequent metabolic breakdown at every age throughout life. Death rates for these diseases are about twice as high for every age group in northern United States as for comparable populations along the Gulf of Mexico. A similar relationship seems to hold for other continents of the earth, although lack of uniformity in mortality records makes difficult so clear a presentation of the differences as is possible in America.

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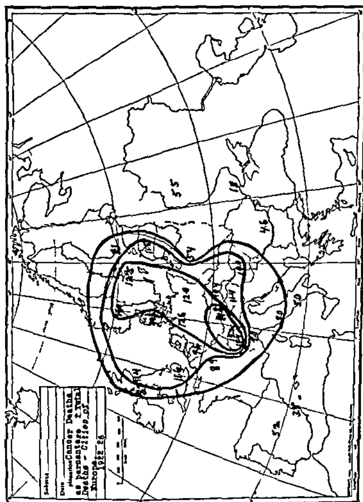


FIG 17 Cancer death rates in Europe

tating effects appear in the earlier decades of life Heart failure from coronary disease is becoming entirely too frequent in the fifth decade and even in the fourth in those same energetic populations that are showing

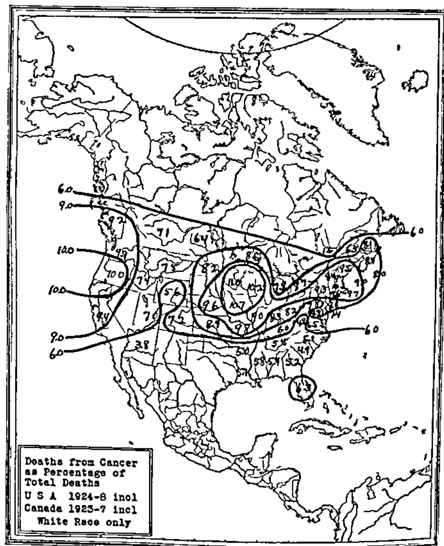


Fig 16 Cancer death rates in America

the highest frequency of metabolic breakdown Negroes of the north show this vascular sclerosis problem in its most severe form, just as they suffer more severely from diabetes With them sclerosis is most likely to assume the malignant rapidly progressive form Negro deaths from arteriosclerotic (non syphilitic and non rheumatic) causes in Cincinnati occur

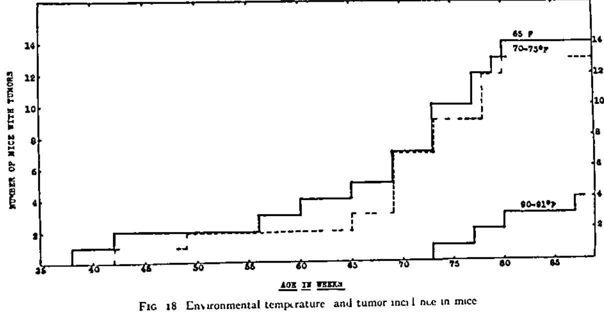


Fig 18 Environmental temperature and tumor incidence in mice

at significantly earlier ages for northern born negroes than for those born in the Gulf States[19] Perhaps the experimental studies now being carried on so actively by various investigative groups will throw valuable light on this problem of vascular sclerosis Certainly little headway can yet be claimed by the medical profession in devising means for its control although it constitutes a really major cause of disability and death in populations of temperate regions

Cancer

Cancer is another major health problem against the inroads of which little headway has yet been made New evidence is now being presented to show that here again is a type of disease showing the same climatic relationships as do the metabolic disturbances All forms of cancer except those of the skin and buccal cavity are more frequent in populations of middle temperate regions than they are toward tropical warmth[20] In fact cancer death rate maps for any continent show a remarkable similarity to those for diabetes (see Figs 16 and 17 for cancer death rates in America and Europe) Use of death rates however is always open to the criticism that diagnostic errors or inaccuracy of death certification may mask the real disease frequency more in some regions than in others Recent experimental proof has been obtained though strongly supporting the likelihood that there is a real climatic factor in cancer production

Fig 18 illustrates the marked suppression of cancer incidence in mice by an environment of tropical warmth Virgin females of Little's dba strain of cancer mice with a normal breast carcinoma incidence of over 50 per cent were subjected to environmental temperatures of 65° F 91° F and 70–75 F With all other factors of existence held constant these mice up to 20 months of age exhibited practically a normal cancer incidence in the room at 65° F but at 91° F there occurred a marked suppression At ordinary laboratory temperatures 70–75° F there was almost the same frequency as at 65° F but with a slight lag in time of appearance In addition to the breast carcinomas 11 of these mice also developed tumors of the lymphosarcomatous type in internal organs Five of these were in the group kept at 65° F five in the 70–75° F group and only one in those kept at 91° F

Tumors not only appeared less frequently and later in the heat but their rate of growth also was markedly slower At 91° F they grew only half as rapidly as at 65° F taking roughly twice as long to kill the afflicted animal This same difference has been found for chemically induced and transplanted tumors in mice except for those of the skin

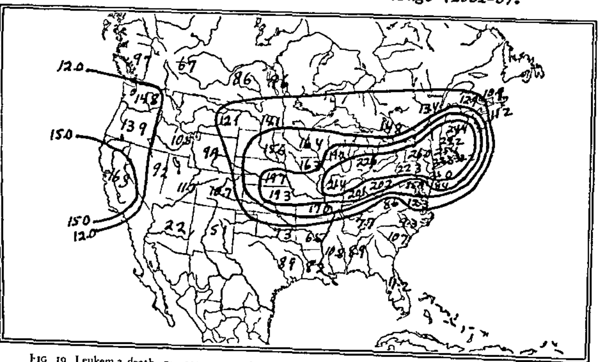


Fig 19 Leukemia deaths per 100 000 population Rural white race only — annual average (1931-5)

Cancer masses grow most rapidly in the deeper tissues of mice kept in the cold but in the heat they grow fastest in the skin This is an important observation for it would seem to indicate richness of blood supply to be a dominant factor At 65° F the deeper tissues need the richer blood supply to support their higher level of metabolism while at 91° F the difficulty of heat dissipation calls for most active circulation through the cutaneous capillaries If the environmental temperature be raised sufficiently to produce fever in the mice and an elevation in general metabolism then tumors of all regions grow more rapidly than in the cold

The higher occurrence rates for skin cancers in people living in warmer climates would thus seem to be due not to greater actinic irritation from the tropical sunlight as has been supposed but more probably to the richer cutaneous blood supply for heat loss purposes and in regions of more active stimulation of the general metabolism the higher incidence of internal tumors would seem probably related to the higher combustion rate and richer blood supply in the deeper tissues

Leukemia

Leukemia sometimes has been considered a form of neoplasia so it is interesting to note that four tumor free mice in the group kept at 65° F showed post mortem evidences strongly suggestive of leukemia Fig 19 also shows the same band of high leukemia death rates across middle temperate latitudes of North America that was found for cancer and the metabolic diseases All in all it does seem that the degenerative neoplastic and metabolic diseases are closely bound up in some way with general tissue combustion level and ease of body heat loss The therapeutic implications of this relationship are many and varied but their consideration will be taken up on a later page

Infectious Diseases

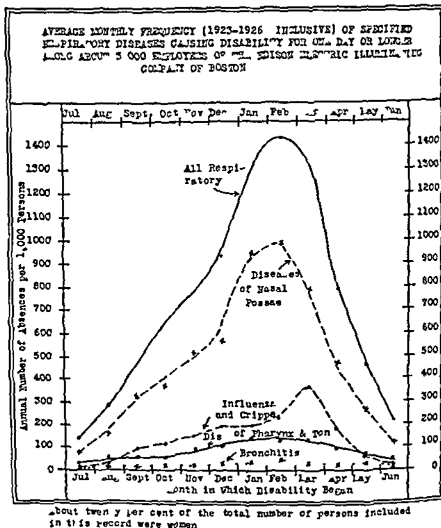
As shown on an earlier page resistance to infection and ability to produce immune bodies seem closely linked to tissue combustion rate in warm blooded animals Difficulty in heat loss enforcing a lowering in tissue heat production causes a sharp decline in ability to fight infection This has been shown to be as true for several infectious diseases of man as for experimental infections in laboratory animals Thus one factor of climate becomes of major importance in infectious diseases There is however a second climatic factor of equally great importance Cyclonic storminess with the atmospheric changes that accompany passage over

ter brings much less of an increase in life's hazards for there storminess is least during midwinter cold The increase in mortality from respiratory infections in the United States from summer low to midwinter high is almost three times as great as it is in similar latitudes of Australia And in the United States unusually stormy winters are accompanied by much greater frequency of respiratory illness and death than are those of lesser atmospheric turbulence Hospital admissions for acute rheumatic fever at Cincinnati show a similar parallelism with seasonal changes in storminess

This relationship of storminess to infections is just as evident on a regional as on a seasonal basis *Acute respiratory infections* and *acute rheumatic fever* are predominantly diseases of stormy regions being worst in the middle temperate belt of cyclonic storms and least troublesome in calm tropical warmth Respiratory disease in the tropics becomes a real problem only in those regions afflicted with cyclonic storms of the typhoon or hurricane type Such regions include most of the Philippine Islands and the eastern Asiatic coast up to Japan those parts of India around the Bay of Bengal most of the West Indies and nearby eastern seaboard of North America and to a lesser degree the southwestern coastal region of Mexico Low pressure storm centers passing over these regions seem to bring much the same respiratory disease problems as are faced by people living in the temperate zone storm belts They do not have the body chilling from sudden temperature change such as afflicts people of stormy temperate regions but the pressure changes alone seem capable of initiating the infectious attacks Careful physiological studies are badly needed in this field of pressure change effects particularly as regards disturbances in tissue water balance Present knowledge in this field is extremely sketchy and inadequate

In order to give a general appreciation of the storm problem over North America there is shown in Figs 21 and 22 the course followed by anti cyclonic high pressure centers affecting the United States during the four year period 1926–29 Each such major high center affects an area 1 500 to 2 000 miles in diameter as it sweeps across the continent From these figures one may get some idea of the relative differences in storm effects man faces in different parts of the continent during the winter and the total reduction in storminess that comes with summer warmth In the summer storm centers cross the continent less frequently travel more slowly and are accompanied by less abrupt and less extensive atmospheric changes At no time of the year do major storm centers cross the southwestern part of the United States or the highland regions of Mexico This non stormy zone expands northeastward during

a given region of successive highs and lows seems in some as yet unknown manner related to the initiation of infectious disease attacks Respiratory and rheumatic infections are perhaps most closely involved in this type of climatic effect but it also influences such other infectious attacks as acute appendicitis and puerperal septicemia



About twenty per cent of the total number of persons included in this record were women

FIG 20 Seasonal variations in respiratory ills

Fig 20 illustrates the striking degree to which respiratory infections are associated with winter cold and storminess in north temperate latitudes Life hazards of all sorts reach a peak at this season for to the infectious dangers of the more violent storminess is added the greater stress of an increased metabolic load In southern hemisphere lands win

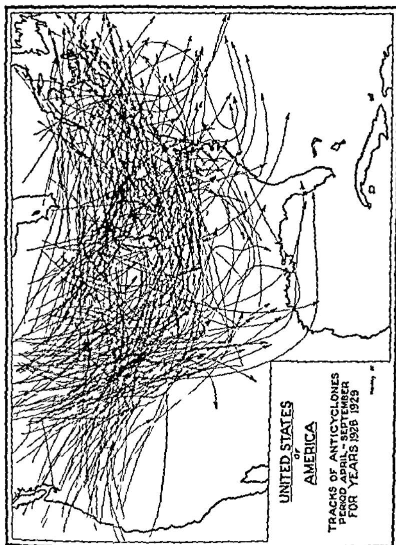


Fig American storm track anticyclone summer

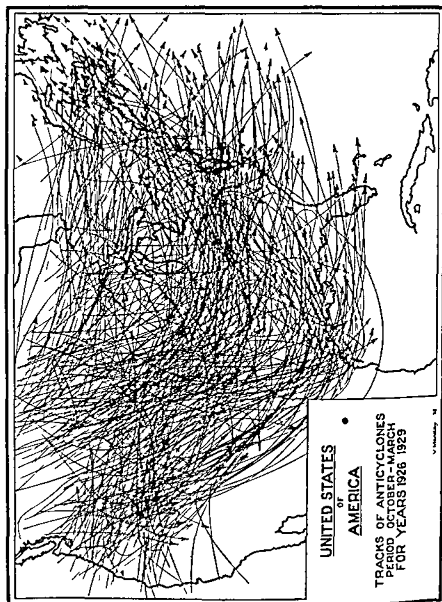


FIG -I Am rican t rm track anticycl n nter

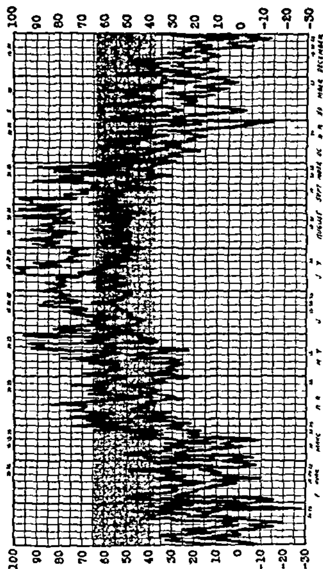


FIG 4 Graph of daily maximum and minimum temperature Bismarck 1935

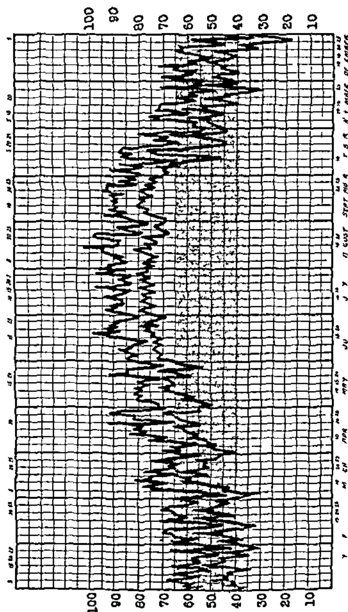


FIG 23 Graph of daily maximum and minimum temperatures Charleston S C 19-5

summer warmth and at this season people of the Old South are left with the stagnant moist heat typical of tropical regions These two storm maps deserve considerable study for from them can be obtained much of the storm health story Figs 23 and 24 depicting the daily tempera-

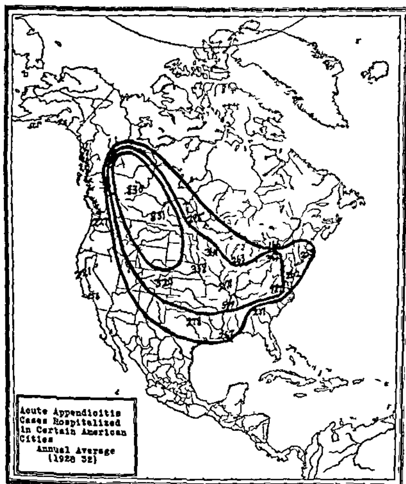


Fig 26 Acute appendicitis cases hospitalized in certain American cities annual average (1928–32)

ture changes through the year at Charleston and at Bismarck give striking emphasis to the differences in atmospheric change that these storm centers bring to the various regions over which they pass Fig 25 shows for contrast the daily temperature behavior in a non-stormy

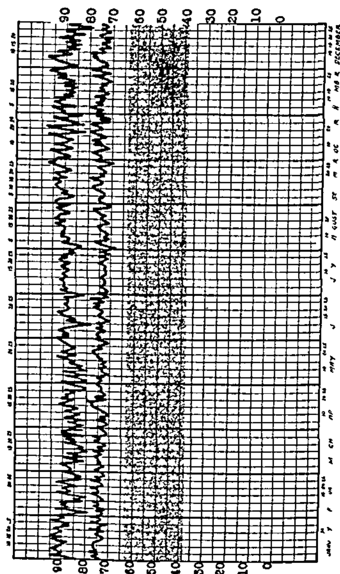


Fig 25 Graph of daily maximum and minimum temperature Manaos Brazil 1914

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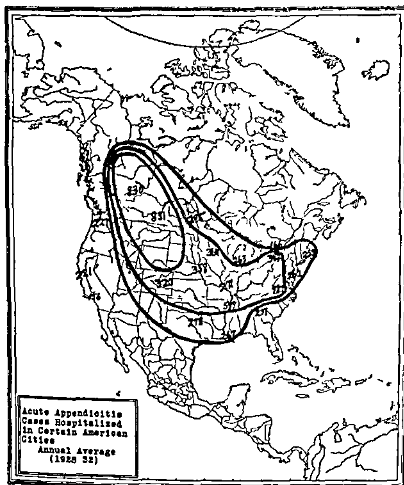


FIG 26 Acute appendicitis cases hospitalized in certain American cities annual average (1928–32)

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tropical region with its endless monotony of successive days of depressive moist heat

It is in the stormy winter season and in the stormy regions of the earth that respiratory and rheumatic infections most severely afflict man

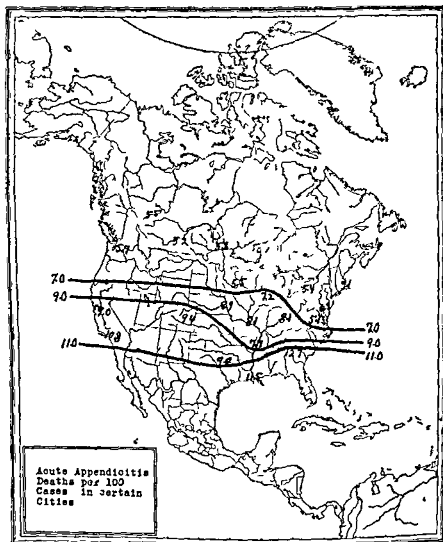


FIG 27 Acute appendicitis deaths per 100 cases in certain cities

kind Benefits of migration of individuals from such regions to non stormy areas will be discussed in the next section which deals in some detail with climatic therapy in relation to various disease conditions from which man suffers

Acute Appendicitis

Acute appendicitis statistics obtained in a limited survey of 25 American cities[12] illustrate well the possible relationships that might be found between climatic characteristics and infectious diseases if morbidity statistics were more generally available Fig 26 hints strongly at a storm distribution of the acute appendicitis attacks with highest rates down the western plains along the major storm pathway from the Canadian Northwest It is in this area that appendicitis becomes a rapidly fulminating disease with quick progress to perforation and spreading peritonitis if not promptly operated upon Nowhere else in temperate regions is it so frequent or severe Only in the worst storm ridden parts of the Philippines and West Indies does it compare in frequency of attacks with this central trough of North America In non stormy regions either tropical or temperate it is a much less virulent and less frequent disease Its relationship to storminess can be shown at any given point by its tendency to occur as waves or epidemics of attacks with the approach or passing of each low pressure center and by the sharp reduction in attack frequency as high pressure areas come along

Regional differences in ability to survive such infectious attacks are well illustrated in Fig 27 showing the steady fall in fatality rate per 100 attacks from the Gulf States northward Here it is the greater ease of body heat loss and more active tissue combustion in the north that brings on better resistance to the infectious attacks The fatality rate mounts with summer heat even in those cooler latitudes where general resistance to infection is highest

Acute Nephritis

Acute nephritis is another infectious disease in which clear climatic relationships can be demonstrated In both Europe and America (Figs 28 and 29) it causes fewest deaths in regions of highest climatic stimulation while towards either tropical warmth or polar cold its death rate rises In the depressing moist heat of tropical lowlands it becomes a really important cause of death

Heat Stroke Heat Exhaustion and Heat Cramps

In addition to the profound effects upon tissue combustion rate and body functions exerted by moderate difficulties in heat dissipation there are also more acute disturbances brought by excessively high environ

mental temperatures Such disturbances are predominantly problems of human populations living in the middle temperate latitudes This is true

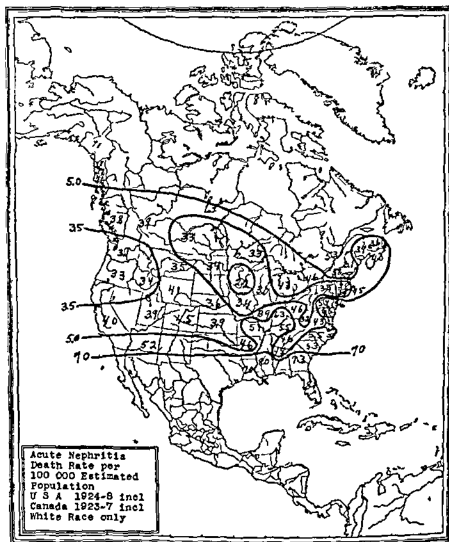


FIG 28 Acute nephritis death rate per 100 000 estimated population U S A. 1924–8 incl Canada 19 3–7 incl white race only

for two reasons both of which are involved in an explanation of the physiology of these excessive heat effects

The first reason for greatest prevalence of acute heat effects in tem

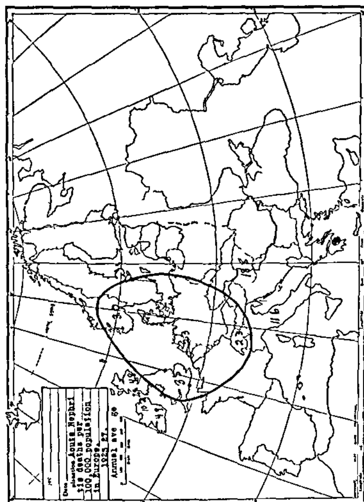


FIG 29 Acute nephritis death per 100 000 population in Europe 1923–7 annual average

perate regions is that there man's own internal heat production is highest and his necessity for rapid heat dissipation greatest. Animal studies[1] under controlled conditions have provided a satisfactory explanation for heat sensitivity in man. Either animals or men adapted for weeks or months to cool surroundings develop a high combustion rate and this proves embarrassing when sudden difficulty in heat loss is encountered. In regions afflicted with depressing tropical moist heat these acute heat effects are uncommon. People residing there have adapted themselves to a lower rate of internal heat production and acute effects are seldom seen except in newcomers from cooler regions. It is in the more energetic population masses of middle temperate latitudes that acute heat effects occur in greatest profusion. Severe heat waves of summer come upon these regions suddenly and sometimes kill thousands of people before their body heat production can be brought down within their capacity for dissipation under the difficult conditions suddenly prevailing. Particularly prone to this embarrassment from the sudden heat are the less resilient sclerotic patients and those of limited cardiac capacity. Increased peripheral circulation to facilitate the loss of internal heat throws a greater burden upon the heart, hence the heat wave dangers for those with heart trouble.

Animal and human studies have shown that 10 days to 2 weeks are required for any considerable subsidence of basic internal combustion in response to external heat. Population masses demonstrate this delay in adaptation by being able to stand considerably more severe heat in August than could be safely borne in June or early July. In fact most heat stroke epidemics occur in early July rather than in the hotter weather of August. But if a severe July heat wave were to be inflicted upon these same populations at the height of their winter activity, its effects would be truly devastating, perhaps as much so as would a North Dakota winter if suddenly inflicted upon the people of Manila or Singapore or Calcutta. It is then the prevailing internal heat production rate of man that largely determines his sensitivity to acute heat effects when faced suddenly with severe external warmth.

The second factor responsible for the greater prevalence of acute heat effects in temperate latitudes is that most severe heat actually occurs there. Dry bulb temperatures of over 100° F are rare in tropical regions except in desert areas, while temperatures above this level are not unusual during severe summer heat waves as far north as the prairie provinces of Canada. Heat deaths and prostration occur mostly in urban and desert regions and for somewhat similar regions. With the dense vegetation of tropical lowlands, and less so in rural temperate areas, the physical sur

roundings of man have a high water content Green foliage is largely water and the high specific heat capacity of water enables it to absorb large amounts of radiant heat from the daytime sun with little rise in temperature Baked earth desert sands and urban building or paving materials have a very low specific heat capacity and suffer a marked temperature rise under the radiant heat load from the sun In desert regions this daytime heat is quickly re radiated off into space soon after sundown but in built up urban areas it tends to be trapped within buildings and to cause progressively higher temperatures as the heat wave persists day after day Building construction in tropical cities takes account of this danger and provides for ample air currents to carry away any such daytime heat that gains access but in temperate zone cities winter cold prohibits this open type of construction and the trapping of daytime radiant heat makes the heat problem for urban dwellers worse with each added day of summer heat wave

The exact mechanism of *heat stroke* production is not understood Patients in a hypertherm chamber develop artificial fever but with free perspiration and without the other evidences of heat stroke In typical heat stroke on the other hand cessation of perspiration seems to be one of the very early symptoms of trouble Sufficiently severe heat will kill anyone normal and abnormal alike but it may well be that the previously normal individual would continue free perspiration to the end while the abnormally heat sensitive person i so because his sweating mechanism quickly becomes deranged Chief difficulty in studying this problem is the lack of experimental animals with a sweating mechanism at all similar to that of man Artificial fever treatments on man have provided some valuable evidence but even this has not been well utilized to elucidate the heat stroke mechanism Patients who fail to perspire freely under such treatment are removed quickly as poor risks for fever therapy

Heat exhaustion while still a direct result of difficulty in dissipation of body heat differs sharply from heat stroke In the latter there is fever and delirium with full bounding pulse and elevated blood pressure while the skin is flushed and dry Immediately important in therapy is rapid heat removal by the best means at hand Heat exhaustion on the other hand usually is characterized by subnormal body temperature cold pale clammy skin low blood pressure and a state of circulatory shock In addition there are other symptoms of acute adrenal insufficiency hyper onicity of the gastroenteric tract with nausea vomiting diarrhea sphincter spasm and painful peristalsis Here immediate treatment should be directed toward raising the body temperature to normal improving the

tone of the vascular system and allaying hyperactivity in the digestive musculature.

It is thus apparent that heat stroke and heat exhaustion represent radically different body responses to external warmth. Correct diagnosis is important because of the sharp difference in type of treatment indicated. Here again we are faced by a lack of knowledge as to why one individual develops the dynamic hyperpyrexia response and another the hypothermic shock reaction. Unfortunately one experience with either type of excessive heat reaction predisposes the patient to subsequent attacks and to troublesome prodromal symptoms with external heat of relatively low order. So far no means has been discovered for overcoming this increased sensitivity induced by a preceding heat attack. Careful avoidance of exposure for the next several years remains the patient's only safe course to follow.

There exists a likely possibility that pantothenic acid deficiency may be a factor in the production of heat exhaustion. The symptoms and anatomical findings in heat exhaustion point to the adrenal cortex as the affected tissue responsible for the exhaustion state. Adrenal hemorrhage in man gives much the same clinical picture except that it is in more acute form. In experimental animals exposed to heat in the author's laboratory adrenal hemorrhages were produced in few instances but intense adrenal congestion was encountered frequently. Recent work[22, 23] has shown that such congestion and hemorrhagic necrosis of the adrenals is pathognomonic of pantothenic acid deficiency in animals, while such deficiency signs have been found much more easily produced in animals kept at high temperatures in the author's laboratory. The possibility does therefore exist that heat exhaustion with its attendant symptoms of adrenal failure may be based upon a pantothenic acid deficiency and that the administration of this material would provide a useful therapeutic aid in the treatment of such exhaustion. The severe heat of coming summers will give an opportunity for trial of such therapy. Thiamine therapy 5–10 mgm daily also seems to make for better heat resistance.

Heat cramps in the skeletal muscles bear little relation either to heat stroke or heat exhaustion. They are due primarily to excessive salt loss during profuse and prolonged perspiration without adequate salt intake. Relief is obtained readily by adding ordinary table salt to the drinking water or by taking it in any other convenient form. Sometimes a heat exhaustion patient will be suffering also from skeletal muscle cramps but usually they are not associated. Laborers in desert heat and furnace rooms are particularly prone to heat cramps because of their excessive perspiration and rapid salt loss.

Sickness and Health Tides

An important point of general medical interest arises from the close association between temperature level and storminess on the one hand and infectious illnesses and metabolic breakdown on the other as set forth in the preceding pages Definite health tides have been found[24] to accompany the periods of warmth and calm that come over the world every few years At these times earth temperatures rise and temperate zone storminess lessens Winter stress is reduced greatly and summer heat increases Human energy seems to decline during such years of warmth for business activity falls off *and the economic machine tends to idle along until cold* and storms again return This relationship between earth weather and economic activity seems to be a true finding More striking from a medical point of view however is the health improvement which regularly comes with these years of warmth and lessened economic activity Huntington[25] *first pointed out this association between improved health* and hard times but Huntington s explanation of the relationship is no longer tenable

Sickness and death rates do decline and calls for medical service are lessened during years of warmth and lessened storminess and as falling temperatures bring increased mass energy and returning prosperity we regularly see again a rising ill health tide These tides in energy and health are similar to the seasonal ones which occur in temperate regions where winter cold and storms regularly bring greater energy but also bring higher sickness rates and death rates Even heart failures non infectious non luetic reflect in their course the lessened stress of these warmer years

While there is little we can do about these tides in weather and health it is well to appreciate their presence and significance Periods of economic depression commonly are associated with an expectation of deterioration in health and general nutrition of the population Even a regular repetition of health improvement in hard times instead of health deterioration has failed to shake the popular expectation It is time the medical profession awakened to the fact that general health is best in those very years when the public is willing to spend least for medical services It is not however that the services of the medical profession constitute a health handicap but that powerful extraneous forces are at work altering the basic environmental factors of existence Careful analysis of the action of these tidal forces on health has helped us toward a much clearer understanding of how environmental factors produce their effects

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ation of many types of infectious attacks particularly those of respiratory and rheumatic types Since respiratory and rheumatic ailments bulk so large as ill health factors in stormy regions it is necessary that this storminess factor be given proper consideration

These are the general principles to be borne in mind when considering climatic therapy for individual cases Physicians should help the patient come to a decision regarding permanent change of residence For most adult people such re location entails major economic difficulties which tend to tie the individual to his present place of abode It is the physician s duty then to help him balance the anticipated health benefits against the deterring economic factors For younger patients not yet tied down the problem is much more simple But in every case it is for the physician to point out the anticipated health hazards and impairments in body function that may reasonably be expected from continuing on in the unfavorable environment and to detail the health advantages of the change Each case will offer an entirely different set of difficulties and problems to be considered And always in these considerations the physician should take an active and sympathetic part as family advisor Let us now take up in some detail the facts upon which his advice should be based in various disease states

Metabolic Diseases

Fairly clear indications of benefit from climatic therapy exist in the diseases of metabolic exhaustion or over stimulation *Diabetes* as a disease is most frequent and most severe in the energizing middle temperate regions where metabolic stress is greatest There severe ketosis and coma are of easy occurrence and constitute major hazards for these patients The disease exists in sub tropical and tropical lands but as a mild non troublesome glycosuria with little or no tendency to severe ketosis Mild dietary regulation usually suffices for the needed degree of control Vascular troubles and peripheral gangrene bother diabetic patients much more in the cooler regions where arteriosclerotic troubles are more common and winter cold further intensifies this hazard of the disease It seems clear therefore that diabetic patients should be advised of the milder course taken by their disease in warmer regions Permanent *migration into subtropical warmth should be advised whenever it is* economically possible for the patient The strong tendency of the disease to appear in children of diabetic parents makes such migration particularly advisable where there are offspring to be considered

Migration for diabetics should consider not only transfer to subtropical

Climatic Therapy

Two cardinal features of climatic effects must be kept in mind when climatic therapy is being considered Probably of greatest importance to man in a given region is the mean temperature level and the ease with which he can get rid of his waste heat of cellular combustion Proper ease of heat loss gives to human health a more dynamic and positive character leading to rapid growth early maturity high fertility, increased resistance to infection and abundant energy for thought and action but *with the heightened cellular combustion rate necessary to support this* more dynamic existence go evidences of stress and breakdown in the body machinery Metabolic and degenerative diseases form the most troublesome health problems only in those regions where climatic stimulation is high

With the slower combustion rate necessitated by tropical difficulties in heat loss existence becomes more vegetative and passive growth and development slow down and a sharp decline in resistance to infection allows infectious diseases to become predominant causes of death Factors outside of man himself also contribute largely to the infectious disease problem in tropical warmth especially better temperature conditions for the growth of bacteria and parasites outside the body and the greater abundance of insect vectors Other important factors while not having to do directly with lowered tissue resistance do depend upon man's lowered combustion rate and lack of energy for thought and for work accomplishment The low level of personal and public hygiene usually existing among tropical peoples unless health measures are initiated and enforced by outsiders from more energizing climates most likely is based upon the debilitating effects of the tropical warmth upon man himself The combination of all these internal and external effects of climate makes the infectious disease problem the major one for tropical residents People of warmer regions who survive infectious hazards to reach more advanced ages do so with much less evidence of metabolic stress than is seen in similar age groups of more stimulating regions Metabolic and *degenerative diseases* diabetes toxic goiter pernicious anemia arteriosclerosis cancer are all much less prevalent in Gulf State populations than in the same age groups in middle temperate latitudes of America Similar latitude differences are to be found in Europe

The second climatic factor to be considered in any intelligent effort to use climatic therapy is the effect of storminess or sudden weather change Although we as yet know little about the mechanism of its effects weather change does seem to be an important factor in the initi

coincide In America that would mean the Gulf Coast well south in Florida or Texas for the winter season Artificial moist warmth if consistently and properly applied should be just as effective in the patient s own home region but it would necessitate an indoor existence for a considerable period at high temperatures and high humidity 90 F and 70 per cent relative humidity or thereabouts

Pernicious Anemia

Pernicious anemia likewise pursues a milder course in tropical warmth while leukemia is almost unknown in tropical and subtropical warmth except in migrants from temperate climates There are as yet no data available however regarding the benefits of climatic therapy in these conditions For those who can move either seasonal or permanent migration to avoid winter cold would seem advisable As with diabetes and toxic goiter regions of moist heat should be chosen so as to achieve the maximum of metabolic suppression and reduction in load on the hemopoietic system

Arteriosclerosis Hypertension and Heart Failure

Arteriosclerotic hypertensive and *heart failure* patients present the clearest likelihood of benefit from climatic therapy Blood pressures in either normal or hypertensive individuals show a decided tendency to drop with even the brief summer heat of middle temperate latitudes This drop usually amounts to about 30 per cent from the preceding winter level giving marked relief from hypertensive symptoms during summer and early autumn Both systolic and diastolic pressures of the author fall about 40 per cent after a month spent in tropical moist heat or after a prolonged summer heat wave at Cincinnati These falls in pressure probably are due largely to loss of vascular spasm but the lowered general combustion rate and lessened load on the circulatory system also may play a considerable part

Recent studies on the production of malignant hypertension and arteriosclerosis in experimental animals has suggested the possibility that vascular spasm in the renal vessels of man may be an important factor in the sclerosis picture It may be for this reason that vascular sclerosis and failure become such dominant health threats in the most energizing and stressful climates and that such welcome relief is brought by even the brief periods of summer heat Fig 15 on a preceding page indicated the marked lowering in the incidence of heart failure during summer

warmth but also escape from cyclonic storminess Acute infectious attacks form the most frequent cause for ketosis onset in these patients and cyclonic storm changes seem to be a potent factor in the initiation of the infections Migration should therefore be to a non stormy and warm region In North America that would mean the Southwest within 200 miles of the Mexican border from El Paso to the Pacific coast Altitudes above 5 000 feet should be avoided because of the relief from the summer heat such elevation brings and the fair degree of metabolic stimulation brought by the wide diurnal changes in temperature Florida and the Gulf Coast offer more depressing warmth than does the Southwest due to the higher humidity of the air but winter storminess and the attendant respiratory infection problem there presents a certain degree of handicap except in the southernmost parts of Florida and Texas

European diabetics mostly to be found living in west central portions of the continent would find their disease much less troublesome and easier of control if they took up residence in some Mediterranean location In Australia benefit would follow northward migration to more tropical portions of the continent In Argentina similar northward migration would benefit those diabetics from the southern cool half of the country, where the disease is more frequent and troublesome

Seasonal migration away from winter cold and storms is advisable for those diabetics who cannot make a permanent change of residence but in such seasonal migration the dangers of too early return in the spring should always be kept clearly in mind This point will be discussed more fully in considering respiratory disease problems

Toxic Goiter and Hyperthyroid States

Toxic goiter and other *hyperthyroid* types of patients except those with definite nodular goiter benefit greatly from migration into the depressing warmth of the tropics or subtropics Even the brief summer heat of northern latitudes tends to quiet down the symptoms resulting from a hyperactive thyroid Definite microscopic evidence of change toward the resting type of secreting cell has been shown to result from even a few weeks exposure of experimental animals to external warmth Hyperthyroid patients should not expose themselves too suddenly to external heat however for their high rate of heat production renders them unduly susceptible to thermic fever Application of gradually increasing external warmth gives best results Since storminess makes little difference to these patients and a maximal depression of internal combustion rate is desired migration should be to regions where heat and high humidity

of all body tissues and should be expected to show most marked evidences of stress in populations living under the most stimulating climatic conditions. Such is indeed actually the case but evidence has not yet accumulated to show whether such patients would be as much benefited by migration to more soothing climates as are the patients with metabolic and hypertensive troubles. Cerebral activity does seem to decline with prolonged external warmth, for psychological testing of college freshmen in lower temperate latitudes gives markedly lower ratings during summer heat than in winter cold, while at higher latitudes the milder summer warmth is without any such depressing effect on mental function. It would therefore seem desirable to try climatic sedation in cases of central nervous exhaustion followed by the mild stimulation of such non-stormy regions as northern New Mexico or Arizona at altitudes of 5 000 to 6 000 feet. Any such climatic therapy should of course be accompanied by very restricted use of tobacco or alcohol and complete abstinence from all stimulants of the caffeine type. It seems advisable also to recommend a high intake of the B vitamins, particularly thiamine, during any such effort at restoration of proper cerebral function.

Infectious Diseases

So far as is known, climatic or weather conditions have little to do with the acute contagious diseases of childhood except as the indoor existence of the winter season brings greater crowding and better chance for contagion to spread. However, for respiratory and rheumatic infections climatic environment seems to be a factor of really dominant importance. Sudden stormy changes, particularly those accompanied by sharp temperature drops, initiate the infectious attacks, while the mean temperature levels under which people live largely determine ability of the body to fight the infectious invasion. Thus rheumatic and respiratory infections occur most frequently in those stormy middle temperate regions where body resistance is highest. This is indeed fortunate, for a North Dakota winter would produce a holocaust of pneumonia deaths if suddenly visited upon a tropical population.

For *sinusitis, bronchitis, bronchiectasis* and a tendency to *repeated colds*, climatic therapy offers very definite benefits. This is again fortunate since only too often these conditions receive little benefit from treatment in the home climate. Epidemics of colds and other respiratory infections continue unabated in populations during stormy middle temperate winters little affected by all the claims of benefit from vaccine therapy, vitamin administration or general nutritional betterment. For

warmth and mention also was made of the similar reduction during certain Cincinnati winters when balmy weather largely prevailed It does seem therefore that climatic and seasonal temperature levels constitute a basically important factor in determining vascular stress and likelihood of functional breakdown and that this fact should receive serious consideration in the handling of patients with a tendency to such vascular troubles

In this matter of cool climate or winter stress man is doubly handicapped He not only feels the urge to be more active in cool weather but each bit of work he does then costs him a greater expenditure of energy than would similar work accomplishment in summer warmth It has been shown[6] that body working efficiency declines as tissue combustion rate rises so that the climbing of a given flight of stairs carries a higher metabolic cost in winter cold than it does in summer warmth Man in cool climates thus is faced both with the urge to be more active and to pay a higher metabolic price for such activity than does the resident of warmer regions It may well be this combination of stresses that is at the basis of his circulatory failure problem in middle temperate regions

At any rate it would seem clearly indicated that any individual showing evidences of the effects of such stress should be advised of these factors acting upon him and of the possible benefits of migration to a less energizing climate and since respiratory infections constitute a major threat to patients with limited myocardial capacity these patients should seek particularly for freedom from winter storminess as well as for soothing warmth Within the United States that would mean southern Florida or the Brownsville region of Texas rather than the non stormy but slightly more stimulating Southwest Advice regarding climatic therapy for these patients would be the same as that discussed on a preceding page for diabetics either in America or in foreign countries and the same precautions should be observed about returning to cool stormy latitudes except during the milder summer months Many people with limited cardiac capacity have died of pneumonia contracted from too early a spring return to a northern home This danger will be discussed more fully under respiratory disease considerations

Nervous Disturbances

For *mental* and *nervous breakdown neuresthenia* and related exhaustion states there exist less clear indications for advice regarding climatic therapy The gray matter of the brain has the highest combustion rate

cause little temperature change but their sharp pressure fluctuations seem to bring on many of the same body disturbances that are associated with temperate zone storm changes Respiratory infections and deaths increase just as much from summer low to winter high in Georgia as they do in New York Only well south in Florida or in the Brownsville district of Texas is there relative freedom from the northern type of winter storm but even these regions remain afflicted with those of tropical origin

Winter migration for relief from respiratory troubles should therefore be directed toward the southwest rather than to the south Moderate elevations within 200 miles of the Mexican border from El Paso west will be found to offer most nearly ideal weather conditions for this purpose Locations for permanent residence might be selected slightly farther north on account of summer heat but probably not far beyond the northern borders of New Mexico or Arizona The point should be stressed that migration benefits soon disappear if the patient returns to northern cold and storms even though complete subsidence of trouble may have prevailed for a considerable period in the non stormy climate For those persons severely handicapped by recurring respiratory troubles permanent change of climate is therefore strongly advised since it offers hope for a more normal existence of health and usefulness

Tuberculosis —This disease deserves consideration from at least two climatic angles even though one today so often hears specialists in this field declare that change of climate offers these patients nothing that cannot be had without leaving the home region The same two principles of climatic effect work in tuberculosis as in other chronic or semi chronic respiratory infections and failure to recognize their value only mitigates against the patient s chance for recovery Acute intercurrent respiratory infections carry serious dangers for people with subacute or active tuberculosis because of their tendency to light up the tuberculosis process and these acute infections come largely with sudden storm changes in weather Hence on this point the tuberculosis patient reduces his disease hazards greatly by migration to a non stormy climate He may receive the same effective nutritional rest and collapse therapy in all regions where proper facilities are available but only in a non stormy climate may he achieve freedom from recurring acute infections

The second point deserving emphasis in tuberculosis relates to those patients contracting the disease in regions of debilitating moist heat or to those with quiescent forms of the disease who contemplate any prolonged sojourn in tropical warmth The marked lowering of tissue resistance to infection in tropical moist heat makes it imperative that patients developing the disease there be transferred at once to a more stimulating climate

most individuals susceptible to recurrent attacks of these respiratory troubles migration to a non stormy region offers the only real hope of relief An occasional patient with chronic bronchitis will be cured by attention to other foci of infection higher up, and a few bronchiectatic patients are helped by lobectomy Therapy for acute sinusitis is in the main beneficial but after the sinus changes have become chronic the patient can look forward to more or less permanency of his trouble so long as he continues on in a region afflicted with frequent waves of acute upper respiratory infections As the years pass he may expect a spreading of the chronic changes to other nasal accessory cavities and to the bronchial tree

An important element in this steady progression of involvement is the frequent repetition of acute flare up with each new respiratory epidemic that comes along or with each body chilling that takes place Persons with these chronic infections are unduly sensitive to chilling and usually make life uncomfortable for those with whom they must live High indoor temperatures and freedom from drafts must be maintained for their comfort Nor is this sensitivity to chilling at all psychic on their part Degrees of chilling that do not bother normal persons in the least may result in prompt exacerbation of their troubles For such afflicted individuals to continue living through northern winters usually means much trouble for themselves and discomfort or damage to others who must inhabit with them the over heated living quarters and face the sharp contrasts between indoor and outdoor air as they come and go

Since medical science as yet has no other therapeutic answer migration out of cold and storms should be seriously considered for such cases If they cannot migrate then steps should be taken to protect them from chilling without endangering the welfare of others in the household by over heating Warmer clothing particularly for the extremities should be the basis of any needed additional protection for the affected individual

Great benefit will come to the chronically afflicted respiratory disease patient from winter migration out of northern cold and storms or from permanent change of residence to the plateau regions of the Southwest Wintering in Florida or in the warmth along the Gulf Coast offers less relief because of two storm factors As shown in Fig 21 cold waves travel well southward down the Plains States during the winter months giving the Southern States then almost as great an atmospheric turbulence as is encountered in the North In addition tropical low pressure storms sweeping westward over the West Indies and Caribbean region bring added instability during the earlier winter months These latter storms

discussed in connection with sclerotic heart failure The indications for migration of rheumatic patients to a non stormy climate are therefore quite evident and emphatic As with the respiratory infections migration should be to the Southwest rather than the South Transportation of rheumatic patients to Florida or Puerto Rico has brought rather disappointing results while in southern Arizona and New Mexico much more complete quiescence of the disease has been obtained The reason for the better results in the southwest probably lies in the year round lack of storms there as contrasted to a winter storminess from Texas eastward almost as great as afflicts the northern states

Migration for patients with rheumatic infections should be permanent if possible since recrudescence is likely to follow return to northern cold and storms If only winter migration is possible then that should even more certainly be to the Southwest since little storm relief will be experienced in the Gulf States at that season For every patient developing definite rheumatic infection migration to a less stormy climate should be considered This is particularly true with the young in whom heart lesions are so likely to develop as the infection continues through the months

Regions of choice for migration of rheumatic patients should be to within 200 miles of the Mexican border anywhere west of El Paso Acute rheumatic fever attacks and deaths are relatively high in frequency throughout the mountain and plateau states even as far south as the northern parts of New Mexico and Arizona[27] Return visits of migrants to former home regions should be made during summer months when storm turbulence is at a minimum

Leprosy —Leprosy is another infectious disease markedly influenced by climatic differences in resistance to infection[8] It exists as a terrible human scourge only in those tropical lowlands shown in Fig 10 as having the lowest order of climatic stimulation In more stimulating regions it ceases to be an active disease and becomes practically non communicable In *tropical moist heat it spreads easily and involves considerable percentages* of population masses in some areas while there was practically no spread from 200 cases imported into the stimulating Minnesota Dakota region during the 19th century migration from Scandinavia Only during the world warmth of the Dark Age centuries did leprosy become really active in temperate zone countries In view of the disease behavior over the earth it would seem wise to segregate patients afflicted with the disease in climatic regions where their own ability to fight the infection will be highest rather than to follow the custom now prevailing of segregation where the disease itself is worst In America that would mean moving

where a higher tissue combustion rate can be maintained The most perfect diet cannot secure nutritional betterment in such patients so long as difficulty in body heat loss interferes with its utilization by the tissues Transfer of these patients from debilitating tropical heat however, should never be to a region afflicted with storms but rather to a such non stormy mildly stimulating climate as is offered at moderate elevations in our Southwest Patients even with completely quiescent tuberculosis should be advised against any prolonged sojourn in tropical heat since the sharp lowering of tissue vitality may bring on a re lighting of the infection

The dangers of migration into stormy temperate regions after any prolonged stay in tropical or subtropical warmth should be kept in mind always For a northerner to make a winter visit of a week or two in the warmth of southern Florida entails no health risk but if he remains there for several weeks his lowered combustion rate renders him liable to seri ous respiratory infection if he return northward while winter weather still prevails This applies particularly to the elderly winter migrant to southern warmth Return to northern homes should be delayed until all danger of winter cold and storms is past Movement of tropical residents to temperate regions particularly those patients run down by debilitating disease should be carried out during summer warmth and with careful protection against weather changes during the entire first winter

Rheumatic Infections — Rheumatic infections seem very closely similar to those of the respiratory system in their relationship to storminess and weather change This similarity may well be more than coincidental for several investigators have felt that rheumatic infections are probably secondary to those of the respiratory system Considerable ground for this belief is provided by the great frequency with which acute rheumatic fever attacks accompany or follow those of the upper respiratory pas sages Whether this relationship be real or only seemingly apparent the strong tendency of rheumatic attacks to flare up in stormy seasons makes it imperative that these patients be protected as far as possible from weather changes Unfortunately they seem most sensitive to barometric pressure fluctuations against which modern housing provides no protec tion Body chilling to which they are also sensitive is as bad for them as it is for patients with chronic upper respiratory infections

The hazards of an active existence in stormy regions especially during winter cold are therefore even greater for patients with rheumatic in fections than for those with respiratory troubles Involvement of the heart with limitation of cardiac functional capacity by valvular lesions further complicates their winter problem This phase of the problem was

heat through radiant channels for summer cooling is more difficult but has operated satisfactorily under both experimental and field conditions

Present air conditioning has brought remarkable therapeutic benefits to one class of human sufferers the sensitization or asthma patients To many complete relief has come by thorough filtering and condition of their indoor atmosphere but this relief does not extend beyond the conditioned space

Air conditioning engineers can readily bring tropical climates to temperate cities or provide temperate coolness in tropical regions It remains for the future to show just what therapeutic use may be made of such facilities The use of artificial moist heat for northern toxic goiter patients was suggested on an earlier page and seems well worth trying Similar artificial depression of metabolism might be tried in other over dynamic states both physical and mental Summer cooling is strongly indicated for the ill during severe heat waves while in the tropics recuperation can be greatly hastened by properly facilitating body heat loss

* * *

It is to be hoped that the reader will see after careful perusal of this chapter that the therapeutic duties of a physician can no longer be concerned simply with the specific treatment of the disease at hand He should look farther afield for the larger forces affecting his patient s welfare and future health And among the outside forces bearing on these more general aspects of existence climatic and weather influences are of great importance The most perfect diet cannot lead to physical vigor and high vitality unless the heat generated in its use can be readily dissipated from the body The physician of the future will therefore need to develop more deeply his interest in and knowledge of climatic and meteorologic influences affecting man throughout his existence in the different regions of the earth

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the National Leprosarium from Louisiana to North Dakota In any such move great care would need to be exercised during the first winter to protect the patients against the unaccustomed vigors of northern winter for they would be highly susceptible to respiratory infections until they had resided for some time in the more invigorating climate This principle already is being put into practice to some degree in Australia but the idea seems worthy of much more widespread application Altitude stimulation in tropical highlands is never far removed from the lowland areas of debilitating moist heat

Air Conditioning

It cannot yet be said just how far man will be able to go in overcoming natural climatic or weather effects by interior conditioning methods It has been shown quite clearly that the biological let-down of summer warmth can be eliminated by adequate artificial cooling to facilitate body heat loss Productivity and physical vigor of tropical workers increases in proportion as the temperature of their working environment is lowered but if such summer cooling is done by cooling and dehumidification of the indoor air then the sharp contrast faced by people entering and leaving such conditioned quarters tends to raise somewhat the same problems that are brought by the outdoor unstable weather conditions of winter storminess

Indoor winter heating if accomplished through air warming also provides sharp contrast between indoor and outdoor air and so increases whatever health dangers reside in sudden atmospheric changes Americans with their careful maintenance of stable indoor temperatures far above outside levels seem only to have accentuated their respiratory disease problems Perhaps the British custom of lower indoor winter temperatures is after all better than what they have termed our over heating

If proper control of body heat loss to prevent winter chilling or summer depression is to be accomplished without producing contrasts between indoor and outdoor air then it will have to be done through radiant channels Very recent studies[29] have shown that radiant conditioning is indeed feasible both for winter heating and summer cooling Certain difficulties remain to be overcome but the great advantages of this type of conditioning almost certainly will bring it quickly to the fore If heat reflective wall coverings be used then individuals in a room can be made comfortable in either winter cold or summer heat through radiant channels alone without regard to air temperatures or humidity Radiant heating in the winter is easily accomplished Adequate removal of body

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CHAPTER XII

HEREDITY AND EUGENICS IN RELATION TO MEDICINE

By CHARLES B. DAVENPORT

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I. GENERAL STATEMENT ABOUT HEREDITY

In order to understand the relations of genetics, or the science of heredity, to medicine, it is necessary to be clear on the biological significance of heredity. If two fertilized eggs, one of a starfish and one of a sea urchin, are placed in a finger bowl of sea water under otherwise favorable conditions each will develop in its own way, one into a young starfish and the other into a young sea urchin. The eggs are both nearly microscopic; they look very much alike even under the microscope. The conditions surrounding them are as nearly identical

contains somewhat unequally distributed particles of varied molecular constitution Always in its center is the egg nucleus formed by the union of the pronuclei of sperm and egg The nucleus contains floating in a fluid a protoplasmic network in which lie granules Before any cell division takes place the granules come together in the form of elongated chromosomes In the act of cell division each of the chromosomes divides precisely so that each daughter cell contains the same chromosomes as the mother cell In the chromosomes are the specific activators of development (enzymes called genes) which control time and place of cell divisions and other developmental processes that eventually lead to the adult form

Nature of Heredity and Environment

One of the commonest inquiries made of the geneticist is as to the relative importance of heredity and environment This seems to be regarded by persons of large experience and vision and especially by those interested in social improvement as a fundamental question It is frequently thought that those interested in human biology and sociology fall into two group the hereditarians and the environmentalists

Such a division is very unfortunate and entirely unwarranted There is in Nature no such contrast Huxley has somewhere described life as the interaction between the internal organism and external world and this interaction extends even to the smallest living cell

The development of the organism and the metabolism of each cell are it is sometimes said determined by genes Others stress the importance of the cytoplasm The truth seems to be that the genes by themselves can do nothing the cytoplasm by itself is so inert as to be ineffective The genes act as catalysts as enzymes which accelerate the chemical processes going on in the cytoplasm determine the specific chemical reaction that shall occur at any moment in the cytoplasm and thus determine the quality of the cell whether it is a bone cell or a muscle cell or a nerve cell or whatever its form and function may be It will be noted that there are certainly hundreds probably thousands of different kinds of enzymes in the gene complex of the cell that there are scores, possibly hundreds of different kinds of molecules in the cytoplasm that at a given moment only a particular enzyme can accelerate a particular cytoplasmic operation Therefore the action of the hereditary units is determined absolutely by the nature of the cell which is environmental to them and the changes that take place in the cytoplasm are determined absolutely by the available enzymes

Similar are the relations between the organism and its environment The organism can do nothing without its environment what the environment

as possible. Yet they develop into very different organisms, of different form and different activity. This difference in the course of development of two fertilized eggs, surrounded by identical environment, can only be due to a difference in internal factors which control their development. The internal factors which control the development of the organism are what we understand as heredity.

This property of the fertilized egg to reproduce the specific form to which it belongs is universally recognized. A child of two Scandinavian parents has at birth a trunk, two arms and two legs, a practically hairless skin and facial features of such and such form because it develops from Scandinavian protoplasm. A child of two Negro parents has a different colored skin and a different form of hair and different features because it develops from Negro protoplasm. This is heredity. Everybody believes in heredity, even those who deny its importance. The two white parents who would be appalled at having a black skinned baby believe in heredity. The person who invests ten cents in a package of seeds marked "double, variegated petunias" has a deep faith in heredity. The only limitation to universal belief in heredity is in respect to its application to particular cases. If a man has his forefinger cut off by a hay knife, we recognize that this peculiarity which he carries through his later life is not due to heredity. If a man is born with four fingers and belongs to a family in which for generations numerous persons have been born with only four fingers instead of five, the special student of genetics will emphatically pronounce his peculiarity to be hereditary. If, however, a single case appears in a family of a child born with a finger which has been constricted or perhaps entirely lost off before birth, we are in more doubt as to whether this is a case of uterine accident, constriction of the developing finger by adhesion to embryonic membranes, or whether there is in this case a genetic hereditary factor. We are familiar also with striking instances of members of the same family who have not been in close contact and who, nevertheless, show similar gestures, idiosyncrasies of speech, or special gifts. Popularly these idiosyncrasies are recognized as hereditary. But when one member of the family is feeble minded, or has epileptic fits, or shows a lack of control over actions such as makes it necessary to remove him from society, then a great difference of opinion arises as to whether these conditions are, or are not, hereditary.

Heredity is not to be regarded as a phenomenon of the same order as a particular disease entity or syndrome. It is something more fundamental and universal than that. It is the internal direction of development.

The developing egg of a particular species, if surrounded by a proper environment and if its internally directing agents are typical of the species and are without lethal factors, will develop in a predictable fashion to produce the specific form with its particular function. The egg is more or less spherical and

kemic and those which are not are fundamentally different and the environment of the leukemic cell is indeed a fatal one Again for the resistant mouse the leukemic cells are no longer a worse environment than normal white blood cells Or looking at the matter the other way around to the leukemic cells a non resistant mouse is a good environment while the resistant mouse is a bad environment but for the normal white blood cells both types of mice constitute a good environment Thus we see that no environment is absolutely good or bad but only such in relation to the particular genetical strain of organism with which it reacts Also the same agency may be genetical from one standpoint and environmental from another standpoint The end result a pathological condition is a chemical interaction between two agents and there is no reason for designating one as the hereditary factor rather than the other

This point of view can be extended for the whole range of human experience In the field of crime the question is often raised whether this is not caused by bad environment This inquiry has no significance Precisely the same environment which is bad for one person and may result in that person becoming a criminal may be good for another person and protect him from becoming a criminal Criminal behavior results from the interaction of a particular environmental set up and a person of particular constitution which causes in that person a criminal reaction On the contrary the same environmental set up might cause a person of different constitution to become a saint We should speak not of bad environment but bad interactions

Sketch of Mechanism of Heredity

General Considerations

Analysis of a chromosome shows that it is made up of a strand of more or less spherical bodies called chromomeres and it is believed that at the center of each chromomere there lies a gene Indeed there are some who believe that they have seen the gene Whether this is true or not the genes probably are among the largest organic molecules and are not far below the range of vision by the aid of the ultra violet light waves

The genes are believed to be enzyme molecules (ferments) It is the nature of each ferment that it acts only upon specific molecules to accelerate their chemical interaction When at any moment there is no pair of molecules present whose interaction can be accelerated by a particular enzyme that enzyme does not function

Starting out with a full equipment of enzymes and with appropriate equipment of building material in the cytoplasm of the egg the catalytic action of enzymes in promoting chemical processes begins and since in the act of cell

does to the organism depends upon the nature of the organism Were 100 children to be reared from birth in an identical environment, being brought in contact with similar cultural conditions, they would still grow up to be very different, because each is highly selective in making use of what the uniform environment provides The "best" cultural condition for one may be the worst for another As a distinguished Frenchman once said, "The equal treatment of unequals is the greatest inequality" Though unequals may be brought in contact with the same external treatment, what use they make of that treatment is highly selective and differential An extreme case is presented by two children one of whom is color blind and the other has sharp color discrimination Looking at the same painting or the same autumn foliage the two will see very different things Similarly, if in a school room one child is deaf, while another has excellent hearing what the two children get from the similar oral instruction of the teacher may well be very dissimilar The deaf pupil may, indeed secure some benefit from the instruction, but does it in a very different way from the hearing pupil Two persons may find the taste of the same substance to be for one agreeable, for the other disagreeable

The same principles apply in the field of medicine During an epidemic of influenza yellow fever or the plague not everybody finds the dangerous destructive agents of the epidemic to be such for him The disease inciting agent is destructive for those organisms which are not prepared to resist it

This principle is illustrated in detail in the case of leukemia in mice as worked out by Dr E C MacDowell with the assistance of Potter Richter, Victor, and others In a colony of mice which had been inbred, brother and sister, for 40 or 50 generations there appeared several who died of leukemia A study of their pedigree showed they were all derived from the same mother If from a mouse about to die of leukemia, blood is taken and inoculated into another mouse of the same strain, but which has not reached the tumor age, that mouse will die from leukemia within a week or ten days The demonstration is complete that inoculated cells carry the power of unrestricted proliferation and this we think of as the "cause of death" But this conclusion is wrong for if a part of the same inoculant that has resulted in the death of one mouse be put into an unrelated mouse of another strain then, apart from an erythema at the point of inoculation there is no reaction, and the mouse continues its life unscathed One sees then that not merely the malignant cells are the cause of leukemia but the susceptibility of the organism or its inability to protect itself against the leukemic cells We are prone to divide the white blood cells into leukemic cells and normal cells It is on the other hand quite as significant to divide organisms into those who are resistant to rapidly proliferating leukemic cells and those who are non resistant For the non resistant organisms the environments of white blood cells which are leu

cally we find that if the father is short in stature has curly and black hair deep brown eyes and swarthy skin and belongs to a race with these characters while the mother is tall and blond and straight haired blue-eyed and fair skinned and belongs to a race which has these characteristics then the offspring will be in these respects much more like the father than the mother They will be short and have curly and dark brown hair dark eyes and swarthy skin

The phenomenon of reappearance in the off pring of certain of the traits of the father s race and certain of the traits of the mother s race is the basis of the principle of dominance which plays a great part in modern genetics A racial trait is said to be dominant when it appears in one of the full blooded parents and not in the other and appears in all of the offspring Dominance has been explained in different ways According to one theory the gene for the trait is present in the germ cells on one side of the house and absent in the germ cells of the other side of the house but in the offspring it is present though in a diluted condition The trait that is on this theory absent is called recessive The offspring of the cited mating do not show the recessive trait though they carry it in their germ cells If now two persons of this origin should marry then one quarter of their offspring will show the recessive trait three quarters will show the dominant trait and of those three quarters two quarters will have it in a diluted condition again The diluted condition is known as heterozygosis and the individuals of mixed origins are known as ' heterozygotic Those offspring which show the recessive trait are homozygotic for that trait as are also those offspring that inherit double dominance of any trait

It is to be said that the foregoing theory is not universally accepted and there are many cases in genetics where it is not applicable The gene responsible for a dominant trait may be opposed by a gene which is not absent but is modified in such a way as to produce the recessive trait The two opposing genes are sometimes spoken of as allelomorphs and of the allelomorphs one is dominant and the other is recessive but neither is entirely absent Heterozygous dominants differ from homozygous dominants in this that the eventual trait is developed in less complete degree than in homozygous dominants Thus in the eye color brown pigment is dominant over the absence of brown (blue eye) but the brown pigment is deeper in the homozygous dominant than in the heterozygous dominant Similarly in the offspring of a Negro and a European the dark skin pigmentation is dominant but less dark than in the full blooded Negro It is believed that where there are two doses of a gene for a particular trait the two doses work twice as fast as and more effectively in creating a character than a single dose

A second principle in inheritance is that different traits are inherited independently of each other Thus for example if one parent is a full blooded

division the different materials of the cytoplasm are sorted out in different cells the nature of the interaction varies in the different cells The different forms that these cells assume must be believed to be due to a difference in the materials upon which the appropriate enzymes work As any chemical process is completed whether it be oxidation or dehydration or other, there is established a particular new molecular set up upon which not the gene responsible for the particular change, but another gene, acts a set up such that the molecules responsible for the original particular change can not act Thus the essential elements of appropriate change, at proper time and place, are provided for

From this point of view the form of man and of the twenty six trillion cells which constitute a man are determined by the genes and cytoplasmic materials stored in the fertilized egg If however the genes or cytoplasmic materials were other than they ordinarily are then there would be produced an organism perhaps but not a man Man as we know him is the visible expression of the interaction of human genes and human cytoplasmic materials Man has not determined the nature of these substances, but the nature of the substances has determined man In just the same way the substance in any fertilized egg determines its specific form, a pig a snake a jellyfish, or a sponge From this point of view the history of the evolution of the animal kingdom is the history of the changes that have occurred in the materials of the germ cells, also, the anatomical and histological analysis of a man is merely a study of the visible end result of the inter workings of the substances that have through various spontaneous or mutative processes in the history of chromosomal evolution come to lie in the human egg

Method of Inheritance of Particular Traits

If two individuals having precisely the same germ plasm should marry, their offspring would be exactly alike and like their parents Ordinarily, this situation is not realized since the germ plasm and the cytoplasm of the eggs that are produced in the same parents are not exactly alike The dissimilarity of the genes is due to the fact that practically all human matings are hybrid matings so that when the germ cells are formed in the body some of them are formed with genes of one kind and others with dissimilar genes It is probable that the cytoplasmic particles are distributed somewhat differently to the different eggs Consequently when a union in pairs of the dissimilar egg cells and sperm cells occurs the offspring differ from each other and are more or less unlike their parents If one of the parents belongs to a race most of whose external characters are very dissimilar to those of the race to which the mate belongs then a dilemma appears as to what the children will be like Empiri

of chromosomes however there is one which has different relation in the two sexes Thus in the female offspring the members of this one pair are identical in their chromosomal content In the males on the other hand the members of this pair have dissimilar chromosomal content In fact one of the chromosomes contains very few active genes The chromosome which is inactive is known as the Y chromosome whereas the active chromosome of the pair is known as the X chromosome The females contain two X chromosomes the male only one X chromosome and one Y chromosome This difference in number of the X chromosomes determines a difference between the two sexes in the activity of the genes in their sex chromosomes and this difference of activity is responsible for the fact that one individual develops into a female and the other into a male with differing male and female characteristics It is true that in vertebrates many of the differentiating characters of male and female can be influenced by hormones early produced by the gonads or sex glands However the quality of the gonads is determined by the difference in the number of X chromosomes In the eggs of insects sex is determined only by the number of X chromosomes there are in them no important hormones secreted by the gonads which influence the sexual characteristics

One consequence of the existence of the sex chromosomes is a difference in inheritance of certain traits that depend upon genes which lie in them Thus a recessive gene of the X chromosome in a male zygote will show itself effective on the soma that develops out of that zygote whereas a similar recessive defect in a female zygote will not show in the adult body because the recessive trait will be covered over by the normal dominant trait There are a number of so-called sex linked traits known in man which appear ordinarily in males but are transferred by females over to their male offspring Among them are color blindness hemophilia and optic nerve atrophy

There are indeed certain characters in man which seem to be influenced not directly by genes but indirectly by the activity of the gonads such are known as sex limited characters Examples are the beard in man and the large spurs and comb of the cock The hen does not lack determiners for large spur or large comb This may be demonstrated by grafting a testis into a young hen large spurs and comb and male coloration soon make their appearance under the stimulus of hormones derived from the male gland

Heretofore we have been considering characters due to a single gene whether dominant or recessive Many traits are due to the cooperation of two or more genes which working together are responsible for a single trait For example the dark skin pigmentation of Negroes is due to the activity of two pairs of genes which probably activate the oxidation of thyrosin to form melanin If the typical number is reduced through hybridization from four to three two or one we have produced the various diluted types of pigmentation known as

Negro and the other a Scandinavian, then the children will all have dark eyes and dark curly hair and dark skin pigmentation If two such children marry, then their offspring will carry the opposing traits of the ancestral races in diverse combinations Thus one may have a dark skin pigmentation, straight hair and narrow nose, another, light skin pigmentation with woolly hair and broad nose or broad nose may be combined with straight hair It has to be recognized, however, that the old idea that each gene produces only a single effect in the developing organism is not strictly correct, but each usually has a predominating effect and various minor effects The reason for this is found in the general considerations given in the preceding section, where it is pointed out that any trait that is developed is developed because of the interaction of one or more genes responsible for this development and the cytoplasm of the egg in which these genes have come to lie and it is clear that the chemical interaction rarely will be limited to a particular and single chemical reaction

What determines that particular traits be dominant or recessive is not definitely explained in the second hypothesis referred to above In general, new and recent mutations result in bringing about a recessive trait in the offspring Most of the developmental defects in the child are due to recessive factors Such are, for example, feeble mindedness, epilepsy, melancholia and many others However, not all deviations from the normal are in the nature of recessive defects Many of the abnormalities in the development of the hand, for example are of the dominant type

The dissimilar nature of the genes in the germ cells of the father and the mother are, as pointed out responsible for the dissimilarity of children However, there is one case in which the development of two children is under the influence of precisely similar genes This is the case of identical twins in which it is commonly believed two embryos arise from the same egg at an early stage of its development These two embryos, therefore, have the same chromosomes and constituent genes and probably very similar cytoplasm However it is to be noted that we can not be sure that the cytoplasm of the cells from which the two embryos arise is identical, and as a matter of fact it not infrequently happens that the embryos which develop with a single chorion are somewhat diverse in form Such diversity in contrast with the ordinary identity may be due either to dissimilarity of the cytoplasm or to differences in the intrauterine environment among others to the stealing by the one embryo of an undue proportion of the circulating blood thus depriving the other twin of its proper nourishment

The genes are found in the nuclei of the germ cells arranged in linear series along the axes of the chromosomes of the nuclei In man there are twenty four pairs of these chromosomes of which one member of each pair is derived from the father's germ cell and one from the mother s Of the twenty four pairs

found in man may be considered briefly with special reference to the part that heredity plays in inducing or modifying them

Resistance and Longevity

When a disease or a death occurs we are prone to assign a cause and in all well organized states there are public mortality statistics which give the number of persons dead and the cause of death The cause of death is too narrowly conceived A person does not die merely of typhoid fever but dies of an inability to resist the development of the typhoid bacillus in his body Indeed the mortality statistics instead of being arranged under causes of death with the subdivision typhoid fever cancer etc might about as properly be arranged under the rubrics Number of persons non resistant to typhoid fever, Number of persons non resistant to cancer etc A text book on bacteriology describes the parasitic organism which is often associated with the disease but says nothing about the organism in which the disease promoting germ is growing The persons who die of a particular disease like typhoid fever are however a selected lot of the population selected because of their physiological and bio-chemical inadequacy to meet the situation presented by germs of disease in the body

Resistance to disease is a subject that has been studied more in plants perhaps than in animals In any case it is recognized of great practical importance by plant and animal breeders By proper methods of breeding there have been produced all sorts of agricultural crops which are resistant to smuts rusts and wilts Similarly there are strains of domestic animals which have been bred resistant to cholera as in hogs to certain protozoan diseases as in poultry and the like In humans no attempt has been made to breed resistant strains nevertheless there are known lines or strains which are highly resistant to diseases This resistance is shown by the fact that the individuals of such lines are rarely ill and that they often live to an advanced age Such nonagenarians are resistant not only to the ordinary germs of disease but also to the degenerative diseases which make their appearance during the involutionary period That longevity is inherited is clear from families that every observer can cite and that are often described in the literature The fact has also been repeatedly demonstrated statistically beginning with the very full studies made by Alexander Graham Bell some twenty years ago Besides a natural immunity and resistance there is of course acquired immunity but this again is a familial trait Persons must already have a certain amount of resistance in order to acquire immunity to possibly fatal disease were there no such initial resistance there would be no opportunity to build up such immunity

sambo, mulatto and quadroon Many, if not most, human traits are due to the cooperation of two or more pairs of genes

Thus we see that the studies of the last two or three decades upon heredity have demonstrated that it is, at the same time, much more definite and much more complex than had been anticipated Much is still to be learned about the inheritance of traits in man The near future will, no doubt, show that just as color blindness and sex production are linked in the sex chromosomes so other traits are linked in others of the two dozen pairs of chromosomes in the germ cells of man The determination of the association of determiners in the twenty four chromosomes is one of the alluring fields of research for the future

II INHERITANCE OF SPECIAL TRAITS,* PARTICULARLY DISEASES AND DEFECTS

INTRODUCTORY REMARKS

The deviations from normality that man shows fall into a number of categories Some of them are of the nature of developmental defects, others are symptoms of disease for the production of which, in some cases, a parasitic organism has been shown to be one factor Others are chemical peculiarities of the body due to defects in metabolism and abnormal internal secretions of various types Without, however, attempting to classify the different causes of the abnormal conditions shown we may consider them in groups according to the organs chiefly concerned

One explanatory remark however may be ventured Because it has been demonstrated that there is a particular parasitic microorganism responsible for the particular disease it does not follow that the particular symptoms shown by the diseased individual are solely dependent upon that microorganism and its activities In a great epidemic, like that of influenza we find individuals in the same house even in the same family, who though they clearly harbor the germs of the disease, show very different symptoms One can hardly think of the parasitic organisms as differing in virulence in such cases rather the human beings in which they are developing differ in their resistance and reactions to the germ Indeed as every farmer knows the harvest of his planting is determined not only by the seed put into the soil, but also by the qualities of the soil itself Similarly, the symptoms that a microorganism will induce in the body depend not only upon the particular physiology of the microorganism but also upon the soil in which it grows namely, the chemical constitution of the individual With these general remarks the different diseases and defects

* Bibliographia Eugenica published as a supplement to the Eugenical News gives fairly complete references to writings on inheritance of special traits

develop far in utero Such intrauterine deaths which amount to from 40 per cent to 75 per cent in strains of mice seem to be due not to any pathological condition in the uterus but to the presence of lethal factors in the genes of the germ cells If both parents carry the same lethal factors then the egg will develop only a little way If one parent only brings in the lethal factor the *child may develop inadequately in the organs affected and early intrauterine* death may be expected A heavy rate of twin production is found where there is multiple ovulation and where the male is vigorous and produces sperm that is without lethal factors

The importance of constitution in twin production is indicated by the frequent cases of particular mothers who produce twins repeatedly One of the most striking cases (which is moreover very well documented) is that of Mrs Clark of Cleveland who by three different husbands had a total of forty two children born over a period of less than 30 years beginning at the age of about fourteen During this period she averaged nearly three children at a birth never had a single child at a time in six instances had triplets and in four instances quadruplets By her first husband she had only one pair of twins by her second two sets of twins and two sets of triplets by her third husband the size of litter produced has averaged much higher It is to be noted that according to the best information available her mother had only twins triplets and quadruplets and her grandmother in turn is stated to have had many multiple births However the earlier generations were not seen since they lived in France

The hereditary tendency to twin production has been followed not only in humans but also in sheep Dr Alexander Graham Bell was able by careful selection of twin breeders both on the male and female side to greatly increase the proportion of twins and triplets produced From that strain on one occasion quadruplets developed in the uterus but caused the death of the mother, since she was unable to give birth to them

The Internal Secretions and Constitution

The importance of the internal secretions has become increasingly recognized during the present century Hereditary factors have been discovered *for a number of the endocrine conditions One of the most striking has been* studied in mice by Dr F C MacDowell A particular strain of highly inbred mice produced litters containing dwarfs Investigation showed that the dwarfs had rudimentary anterior lobes of the pituitary gland Associated with this were an inactive thyroid gland and suprarenals of which the cortex was quite inactive The gonads of these animals also functioned inadequately By injecting into the dwarfs the hormone from normal pituitaries the growth of

The Allergies and Vitamin Insufficiencies

During the present century there has developed a clear knowledge of the anaphylactic reaction and of the allergies which are associated with it It has also become clear that the allergic reactions are highly specific in their incidence, that while in certain families there is a wide spread tendency toward hay fever or eczema following inhalation of certain proteins or the ingestion of particular foods other families are quite immune to such irritating agents.

As for vitamin insufficiencies a study that was made at the Eugenics Record Office of the incidence of pellagra in Spartansburg S C showed very clearly that the disease ran a virulent course only in certain families and, indeed, in cases where severe effects followed these were of different type in different families There were families characterized principally by dermal symptoms, others by intestinal symptoms, others by symptoms of the central nervous system

Similarly, the ability to resist the insufficiency of particular vitamins seems to vary in different individuals and this difference probably has a genetical basis There are some persons more tolerant of insufficiency of vitamins A or B for example, than are others

Twin Production

The number of simultaneous ovulations in a single female differs greatly in different animals running all the way from the condition in oysters where a hundred million eggs may be laid simultaneously to the condition found in many mammals and particularly in groups of primates where usually only one or two eggs are ovulated at the same time In humans about one labor in 100 results in twins about one in 10 000 in triplets the higher numbers being relatively much rarer still The tendency toward twin production depends upon the constitution of the parents It is necessary, of course, for twin production that two eggs should be simultaneously ovulated but of such simultaneous ovulation only a small proportion give rise to twins This follows from some studies made many years ago by Leopold who found that about 10 per cent of women s ovaries showed two recent corpora lutea and therefore two recent double ovulations Although as stated only 1 per cent of labors are twin producing the discrepancy between a 10 per cent ovulation and a 1 per cent twin birth is to be ascribed in part to the male Indeed there have been published a number of observations indicating that the male is not less responsible for the production of twins than the female consort The explanation of the deficiency is in part the failure of both eggs to be fertilized but even more important is the failure of a certain proportion of the eggs to

ABNORMAL GROWTHS

All vertebrates and particularly man are subject to extraordinary localized growths in the body, especially of the adult While it is well known that certain families are especially apt to form these tumors still the method of inheritance has not been definitely ascertained in the case of human and it is certainly particularly complicated by the random mating of humans Light upon the factors responsible for tumor growth is thrown by studies made by Dr F C MacDowell on leukemia in mice In a strain of mice highly inbred brother and sister for forty generations there appeared some individuals that died of a disease diagnosed as leukemia These were all traced back to a single mother in a line known in the laboratory as C58 When the leukemic cells from a mouse progressed in the disease were inoculated into an unaffected mouse of this strain even before the ordinary age of incidence of leukemia the inoculated mouse died usually within a week If however some of the same inoculant was put into mice of another strain such as that known in the laboratory as SL there was only a slight reaction at the point of inoculation but no tumor was formed, or if a slight tumor appeared it quickly vanished It was obvious that the soil was different in the mice of this particular strain of C58 and in the SL strain and that the soil of the latter did not permit the growth of the leukemic cells If a mouse of the SL strain be mated with one of the C58 strain then the offspring are susceptible and further studies indicate that a single factor is responsible for the susceptibility This fairly clean-cut result was possible because of the nature of the inbreeding to which the mice had been subjected and in consequence of which they had become genetically nearly pure Naturally in the young of mice bred haphazardly one can not predict the susceptibility and indeed all susceptible mice would probably prove to be heterozygous and produce susceptible as well as resistant individuals This latter condition is exactly the one we find in humans where resistant and non resistant strains have been combined for an indefinite number of generations and two susceptible genes from the two parents will only occasionally come together in the fertilized egg or the 'zygote' It is probably on this account that statisticians have not been able to show an inheritance of a tendency toward tumor growths between parents and children Nevertheless the evidence is clear not only from the case of MacDowell's mice but from other confirmatory evidence that there is such a thing as natural resistance to tumor growth and natural susceptibility What ever the factor is that gives resistance whether a particular enzyme or other factor is not as yet known It is of course quite possible that one might build up a resistance to tumor growth in an organism by appropriate technique

Among tumors whose inheritance has been more or less well studied are the

the sterile dwarfs was promoted, they became nearly normal in size, and they also became sex functional Autopsies revealed that the thyroids and suprarenal cortex had become active, though the anterior lobes still remained rudimentary In this strain of mice the dwarfism appeared to be due to a single recessive gene Similar studies by Riddle and Benedict have shown that in particular strains of pigeons the activity of the thyroid gland, as measured by basal metabolism is high, in other strains it is low In general, the developmental defects which are due to endocrine disfunction may, in turn, be ascribed to a more remote genic defect which is responsible for that disfunctioning This genic defect passes down through the generations

One of the most striking of the endocrine effects has to do with the build of the body Body build runs the whole gamut of possibilities from very slender to very fleshy and obese These conditions of build are believed to be highly influenced, if not controlled by endocrine conditions To be sure within limits, body build may be influenced by food intake On the other hand certain strains will not tolerate excessive food intake and, consequently, remain slender Studies made at the Eugenics Record Office on inheritance of body build indicate that there are two or more genes responsible for the result that where both parents are slender the children are typically slender, that where both parents are fleshy the children are mostly fleshy, but some of them may be of intermediate or slender build The pituitary and the thyroid both influence body build and perhaps other endocrine glands do also Since the anterior pituitary gland influences the growth processes and also the development of the gonads insufficiencies in the activity of this gland result in individuals who are overweight and in whom (especially the male) the secondary sex characters are underdeveloped

There seems to be, also as Kretschmer pointed out many years ago, a certain relation between body build and form of psychoses Thus, in those individuals in which the psychosis is of dementia præcox type, the individuals are prevailingly of a slender, 'asthenic" type, whereas in the manic depressive psychosis the victim has a robust, pyknic build Extensive studies have been made upon body build in relation to psychoses Kretschmer s findings have been repeatedly confirmed However the work which has been done has been for the most part non quantitative The studies of Wertheimer (1926), done in association with Dr Adolph Meyer of Johns Hopkins University, lead to the conclusion that this relation of constitution to psychoses has been exaggerated

The failure of the secretions from the islands of Langerhans of the pancreas is now known to be an important factor in the production of diabetes but numerous studies have shown this to have a hereditary factor, as for example those of Gossage (1908) of Williams (1917), Pincus and White in Joslin s clinic (1933), and others

other cases increased to 6 or more Always in these cases there is a dominant factor which interferes with the normally precise definite number of digit formed on the margin of the paddle at the tip of the embryonic limb in other cases the bones of adjacent fingers may be grown together producing the condition known as syndactylism This is found also in poultry The phenomenon has been treated monographically in the Memoirs of the Galton Laboratory of Eugenics Part 6 Even the details of forms of hand and feet are modifiable by hereditary factors Such modifications arise as crooked fingers double jointedness, and variations in the relative length of the first and second digits of the foot and the second and fourth of the hand

The bones of the hand are especially liable to defects thus ankylosis of the phalanges has been repeatedly described A defect of this sort has been traced by Cushing through seven generations in the United States and by Drinkwater through fourteen generations A related defect is brachydactylia abnormalities of length of the metacarpal bones The fourth metacarpal seems to be especially apt to develop imperfectly possibly due to an imperfect development of the distal epiphysis In the formation of the carpal bones hereditary factors govern as shown by J W Pryor who has traced the order of development of carpal bones in single members of various families When the order of development of the carpal bones differ in one and the same families there is apt to be a resemblance in these sequences of development

The form of the skull is a racial characteristic and details in size and proportions of the head are notoriously found in families The heredity of the cephalic index has been studied by G P Frets

Muscular System

While the muscular system probably has been less completely studied from a genetical point of view than the other systems of the body yet to it have been ascribed inherited deviations from type For example the suppression of the palmaris longus muscle of the fore arm apparently is inherited as a dominant Its absence is more frequent in Europeans than in Negroes Numerous abnormalities are due to defects in the nerves that innervate the particular muscles Thus peroneal atrophy has been described in extensive families as for example by Macklin and Bowman 1926 in 101 descendants of an emigrant to Canada This defect behaves as a dominant The most extensive study of myotonic epilepsy which shows the symptoms of spasms in various muscles has been afforded by Lundborg 1913 who described 2 232 individuals in seven generations The disease is inherited as a Mendelian recessive Myotonic distrophy waste of muscles owing to nervous defect takes on various forms which are apt to be found to be repeated in families where an at

following multiple neurofibromatosis, in which the susceptibility is dominant also multiple telangiectases and polyadenomata of the rectum

Skin diseases that are likewise inherited as dominant traits are epidermolysis bullosa, ichthyosis, keratosis, and persistent hereditary edema All of these skin tumors may, on occasion, pass into malignant sarcoma, which thus shows again its hereditable basis

Skin Diseases

A large number of skin defects and diseases such as albinism birth marks (nævus) keratosis, psoriasis, anonychia, hypotricosis, seborrhœa, have been shown to depend upon hereditary factors Usually there is a dominant factor responsible for the defect The evidence for inheritance of diseases of the skin has been presented by W H Siemens in a large number of papers Heavy pigmentation in the skin was found in the negro race dominant over light pigmentation as in Europeans apparently there are two (double) factors responsible for the deeper pigmentation The mulattoes have only one (double) factor and quadroons only one The tendency to early baldness, which has been regarded by many as simply an accidental disease has been shown to be inherited as apparently a sex limited character The baldness tends to run in different families in particular types, and some, or all, of these types are found as specific characters in different species of primates, as Gerrit S Miller points out Scar tissue reacts differently in different races of mankind, forming keloid tumors in negroes

Skeletal System

The development of bone is a complicated process that has a long phylogenetic history reflected in its complicated nature Especially the long bones are subject to great variation depending upon the activity of certain genes that are responsible for their full development Sometimes the bones are formed in abnormal fashion as for example in brittle bones where the Haversian canals are improperly formed or absent Inheritance of this condition has been described in Bulletin 14 of the Eugenics Record Office In other cases the long bone fails of expected linear development The consequence is that the legs and arms are abnormally short as one sees in achondroplastic dwarfs Inheritance of dwarfism has been described in the 'Treasury of Human Inheritance by Rischbieth and Barrington, and reference is made to that publication for further details

The number of digits is subject to hereditary abnormalities Thus in poultry and the lower mammals the number may be reduced to 4 or 3 and in

absence of a genetical factor that prevents mental deterioration and schizophrenia following the incidence of mental assaults While for many Freudians the exogenous factor is alone to be considered yet the high incidence of dementia præcox in particular families and its entire absence in others not less well protected from such untoward conditions demonstrates that the constitution of the individual must also be considered

In case of depressive insanity it is probable that more than one factor is involved There is reason for thinking that the lack of control which shows itself in great emotional output and excitability under comparatively slight stimulus is partly due to the presence of some genetical factor which inhibits self-control while depressions are due partly to the absence of certain genetical factors that are essential to calmness under ordinary circumstances Again the tendency to dipsomania nymphomania pyromania and the other obsessive neuroses seem to be due to the absence of particular genetical factors responsible for control Dipsomania seems to be dependent upon a sex linked factor shown only by males but transmitted through daughters In studies on crime we are apt to look exclusively to exogenous factors such as bad companions A broad view of the matter requires us to consider also the constitutional factors in which certain individuals find agreeable the stimulus derived from such bad associations In crime we must look not only at the conditions under which it was performed but also to the nature of the individual whose behavior was so bad In the case of the nomadic trait which is found in vagrants as well as sometimes in persons of wealth and culture there is much evidence that this is inherited as a sex linked trait (Bulletin Eugenics Record Office No 12 1915)

Among the more strictly nervous diseases the history of Huntington s chorea has been perhaps more completely worked out than any other It has been possible to trace this disease in certain of our families through ten generations and to show the way in which the germ plasm carrying the defect has migrated from South rn New England and Long Island to upper New York State Vermont Ohio Michigan Wisconsin Kansas Nebraska California Oregon and other parts of the United States (Bulletin Eugenics Record Office No 17 1916)

It is impossible in available space to go into details concerning all of the nervous diseases which have a genetical basis Speech defects such as stuttering and stammering have been shown by Bryant Estabrook and others to recur in strikingly high incidence in particular families Numerous paralyses of special organs some of which have been referred to in the chapters on Muscular System have repeatedly been shown to have hereditary bases

That tendency to self-destruction has a genetical basis is sufficiently demon

tempt is made to trace them Hereditary tremors have been described in animals as for example by Riddle in pigeons where 46 affected individuals occurred in a particular strain Large pedigrees have been secured for human families by a number of authors Finally small muscular deviation, such as produce face dimples, show clear dependence upon hereditary factors

Nervous System

Above all other systems of organs, the control of the nervous system by hereditary factors is of the greatest moment to human society and to the progress of civilization, for the constitution of the nervous system, and its reactions to internal secretions and to other bodily conditions determines conduct, behavior, and to a large extent the interaction of man on man and race on race These hereditary nervous factors determine emotions and aspirations, and the control or absence of control of instincts and, consequently, the individual s fitness as a social being

That the development of the brain with its accompanying intellectual capacity is determined by the absence of one or more factors that make for normal development has been shown again and again in the innumerable studies that have been made upon the feeble minded A great many families have been studied in which feeble mindedness occurs in a high percentage of cases and the results published by Goddard (Kalikaks) Danielson and Davenport (hill folk), Estabrook (Nam family and the Jukes), Finlayson (Dack family) and many others Such strains with mental defect are particularly apt to be found in less highly developed communities, such as occur in some mountain valleys The isolation in these parts is apt to lead to consanguineous marriages and in consequence in such strains to a large proportion of feeble-mindedness due to the same factor or factors When both parents are feeble minded typically all of the children are feeble minded also, though some exceptions occur where the feeble mindedness is due to different types of defect.

Often associated with feeble mindedness is the tendency toward epileptic convulsions of the degenerating type a tendency which shows itself usually at adolescence Studies of this subject have been published in the Eugenics Record Office Bulletin, 1911 and by Romer and by Hermann In the typical institutional cases the epileptic symptoms seem to be due to the absence of a factor that makes for nervous control Tendency to migraine has also a clear genetic factor in many cases and there is a remarkable concurrence of it with epilepsy in certain families

All types of functional insanity seem to depend upon genetical defects Of these dementia præcox has been studied most carefully from a genetical point of view by Rudin and co-workers This depends apparently upon the

have been recently studied through support from the Otosclerosis Committee of the American Otological Society by C B Davenport Bess Lloyd Milles and Lillian B Frink whose results appear in the Archives of Otolaryngology 1933 Heredity is complex, depending on two or possibly more pairs of factors

Idiosyncracies of taste have been discovered recently and found to have a hereditary basis, by Snyder and by Blakeslee (both 1931) For example phenyl thio-carbamide gives a bitter sensation in some human strains in others none at all

ALIMENTARY SYSTEM

Within the last few years evidence has accumulated of the familial basis of some of the defects in the food canal and its adnexa Very obvious is the recurrence of inheritance of harelip and cleft palate in families The inheritance however is complex This matter has been well analyzed by J Sanders (1934) dominant inheritance has been found through twelve or more generations

Numerous studies have shown that there is a genetical basis for gastric and duodenal ulcers A hypersensibility of the intestinal mucosa to chemical and mechanical irritation has been described by Jungling (1928) The tendency to production of gall stones is also one which depends upon a hereditary chemical constitution

RESPIRATORY SYSTEM

That there are hereditary or racial factors present in the mucous membranes of the nasopharynx there can be no doubt Indeed Undritz (19 8) concludes that inheritance is the rule rather than the exception in oto-rhino-laryngological diseases It is notorious that among colored persons there is a relative resistance to diseases that enter the body through the nasopharyngeal portals which are so ill defended among whites Adenoids tonsillitis and diphtheria are much less common in our colored population than in whites despite the superior sanitation on the whole of the latter race in this country

In respect to the pneumonias it is clear that their onset is due to a reduction in bodily resistance In different human strains there is much variation in this natural immunity and one finds as Pearl has demonstrated that tendency to pneumonia is a familial tendency To be sure both conditions of life preceding the disease and age play an important part in the incidence of pneumonia but back of all of these is the variability in ability to resist the multiplication of the pneumococcus germs

strated by the tendency to recurrence in particular families and even, in them, of a particular type This matter has been discussed by Davenport in Carnegie Institution Publication No 236 Sometimes the tendency to suicide is a strong impulse generally associated with manic temperament, and is thus of the type of a dominant trait In other cases the suicide occurs in deep depression, and such depressions are associated with a recessive condition, as mentioned above

Not only those abnormalities in the nervous system and its output which society regards as defects but also those other nervous and mental peculiarities which are commonly spoken of as special gifts show the hereditary factor Though this is not a matter primarily of medical interest, still attention may be called, in passing to the evidence of inheritance in the factors that make great fighters, great mathematicians, great musicians great writers, painters, explorers, missionaries, clergy, physicians and the rest

Sense Organs

The eye is subject to scores of defects in the course of its development and the hereditary recurrence in particular families of these defects has long attracted the attention of ophthalmologists The most recent bibliography of these defects is that prepared by the late Lucien Howe, published as Bulletin No 21 of the Eugenics Record Office The list indicates which of these are inherited as dominant which are recessive, and which are sex linked Of course the method of inheritance of many of these traits is more complex, depending on two or more factors Great advances in our knowledge of inheritance of eye defects have been made by A Vogt of Zurich, and findings in this field have been summarized recently by P J Waardenburg

Ever since Alexander Graham Bell published his "Deaf Variety of the Human Race (Memoir of the National Academy of Sciences 1883), it has been clear that certain forms of deafness depend upon hereditary factors However deafness is not a biological entity, but only a symptom It may depend upon various genetical factors The genetical background probably is often complex It is necessary to distinguish sporadic congenital deafness and deafness occasioned by syphilis The latter is of the nature of an accident, while the former depends upon genes One type of deafness otosclerosis is primarily a bone defect, but functionally belongs to the present category Otosclerosis or progressive hereditary hardness of hearing is due to abnormal osteogenic changes in the otic capsule and the margins of the fenestra ovalis (which is closed by the base of the stapes) so that the stapes is firmly ankylosed in such fashion that vibrations are no longer conducted by the auditory ossicles but better directly through the bones of the head Genetic factors in otosclerosis

III APPLIED EUGENICS

Now that we know that the development of the physical mental and emotional traits of man, his resistance to disease and his normal functioning are determined very largely by heredity it follows that reasonable human beings should act *in accordance with this knowledge Our social difficulties are largely* due to the presence in our population of feeble minded or paranoiacs of those lacking social instincts of those with little control over the emotions Our present methods of dealing with these social disturbers are various In a primitive society we may punish scorn or pity the individuals according to our individual nature but these reactions do little to solve our problem More effective is the segregation of such persons for a longer or shorter period but it is the custom eventually to return such segregated individuals after some years of training to the community Since their constitution has however not been altered they will tend to return to their anti social conduct By releasing segregated individuals at a time when the reproduction urge is strong we permit the reproduction of their traits

An appreciation of the danger of reproducing inherently defective germ plasm has led many of our states and other countries to attempt to exercise some control over this reproduction All states have indeed recognized their right and duty to attempt to control matings Thus we have laws against the mating of the feeble minded epileptic insane of cousins and of inter marriage between different races (Eugenics Record Office Bulletin No 9) These laws have however primarily a legal import rather than a eugenic one and moreover they are inadequately enforced Something could be done to improve present conditions if a greater control were exercised over matings by parents or older persons as is done more satisfactorily in other countries than in ours In the absence of other adequate control of matings many states have found it advantageous to put on the statute books laws permitting sterilization of the genetically defective Over one half of the states of the Union have had such laws in the past at present about twenty two of the states carry them Of all these states California has performed more sterilizations than any other Up to 1929 indeed 6 25 sterilizations had been performed in the California State Hospitals, and 1 488 in institutions for the feeble minded In Canada Switzerland Denmark Germany and some other countries sterilization laws are in effect There has been some question as to the social consequences of the releasing into the general population of sterilized individuals The evidence however indicates that such sterilized persons do not become the focus of immorality The whole social aspect of sterilization is treated adequately by E S Gosney and Paul Popenoe in their book Sterilization for Human Betterment' (1929) Statistics concerning sterilization in different states have been

Circulatory System

The heart and blood vessels, the blood itself, are all markedly under the control of hereditary factors There have been described families where the children at birth are more or less cyanotic, with imperfect development of the valves of the heart A case is described by O Bourwinkel (1910) There is reason for believing that a tendency toward degeneration of the walls of the arteries as well as hypertension depend upon constitutional factors A chapter on heredity of arteriosclerosis has been published in a book on that subject by the Josiah Macy, Jr Foundation

Hemophilia, which depends upon the absence of the enzyme largely responsible for the production of the clotting elements of the blood, has been shown repeatedly to run in families in a sex linked fashion One may conclude that the enzyme responsible for this clotting is in this sex chromosome In affected families the males alone show the condition but do not transmit it to their sons as they transmit no sex chromosomes to the sons, but they do transmit the affected chromosomes to their daughters, who show no symptoms and these daughters may transmit the defect to their sons

Variations in the elements of the blood stream are numerous and some of these have been shown to have a hereditary basis The inheritance of tendency toward leukemia, or a great excess of the white blood corpuscles, has been already described Families with pernicious anemia have been described by O Schaumann, (1918) and other Scandinavian authors Similarly, polycythemia has been traced through generations by E Engelking (1920)

Summary

The above review of diseases and defects shows sufficiently that the hereditary factors present must always be looked for even though these diseases may never occur without the presence of a particular microorganism, for the microorganisms can not be regarded as the sole and effective cause of these diseases or defects We must believe that the constitutional factors prepare the soil and the nature of the soil determines the nature of the harvest, that is the symptoms, which the seed sown upon it will produce The medical man who neglects in his consideration of diseases and defects the genetical factors, will never succeed completely in accounting for the phenomena with which he has to deal Heredity is not something occasional and special Heredity determines the very nature of the organism both the normal organism and the organism that deviates from the normal Only pathologists who are willing to admit that there is a disease apart from the diseased organism can decline to consider the man as well as the parasite that is one of the factors in producing disease

upon carried their propaganda into the higher social stratum which was already reducing the size of families to a minimum with the idea that were their teachings effective in the higher levels a fashion would become established which would become adopted in the lower levels There is however as yet no satisfactory evidence that the propaganda is working out in any other way than to encourage the more thrifty to diminish still further the number of their children Thus it may well be that the birth control propaganda in this country is diminishing the proportion of the more effective children born It would seem desirable rather to encourage the more effective stock to have larger families than to extend more widely the principles of restriction of reproduction Such stimulus might be given on the one hand by appealing to higher ideals and on the other in economic ways by reducing taxation and inheritance levies in proportion to the number of children in the family

A predominance of the fit will not be maintained merely by increasing the number of offspring but also by increasing the number who survive to marry, and in turn become progenitors An intelligent society will therefore do its utmost to encourage the survival of its fittest strains and will be more concerned therein than in securing the survival of the children of inferior strains The appeal sometimes made by social workers for funds to diminish the mortality rate of children of lowest social and intellectual level may well fail to arouse enthusiastic response

Control of matings and of fertility is only part of the problem of securing the highest proportion of effective persons in the population Until recent years the matter of immigration has been of importance in connection with this aim In the early years of our immigration there was little selection of immigrants and it was possible for European countries to exile to the United States those convicted of minor offenses and even sometimes of important crimes Also attempts were made to bring large numbers of the cheapest labor from Furope and even from Asia to help develop our resources Importation from Asia was early put a stop to Only recently has a marked restriction been made on immigration from the lowest economic stratum of Europe Today we exclude the feeble minded and the criminalistic For the moment the whole problem of immigration to the United States has become less important owing to the fact that the United States has become an old country and is already well filled Our resources have become more than adequately exploited so that the country offers less lure to the prospective immigrant *At the same time the opening of* large areas in South America and the better economic outlook there is diverting the stream from the United States to that continent If and when the immigration tide sets again towards North America it is to be hoped that an adequate selection will be made of such immigrants to insure the highest possible quality of our future citizenship

published by H H Laughlin in Eugenics Record Office Bulletins, and elsewhere and sterilization is more and more becoming recognized not as a punitive but as a eugenic measure

The prohibition of marriages between cousins has been placed upon the statute books of over one third of the states in the Union (Eugenics Record Office Bulletin No 9, 1913) Apparently the laws have been thus passed because of the experience of legislators with particular cases in which defective offspring have arisen from such close matings Such legislation does not seem to be in accord with our present biological knowledge It has now been demonstrated by *geneticists, that cousin marriage per se does not lead to defective* offspring However, on the one hand it increases the incidence of defective offspring, where there is gross recessive defect in the common stock as for example, feeble mindedness epilepsy and other types of insanity On the other hand, cousin marriage is a very valuable means of perpetuating and even increasing the general developmental vigor of the children where the common stock is without such gross defect The case of Charles Darwin, who married his first cousin Emma Wedgwood, and produced five sons who became leaders in science, invention, and economics in Great Britain, is a case in point The remarkable group of Walcotts and their kin in Connecticut, which *furnished a* long line of Governors of the state of Connecticut were the product of cousin marriages To make use of our knowledge of genetics in such legislation it were better to provide that a marriage between cousins should not be permitted without a certificate from a state Eugenics Board after an examination of the pedigree, to make sure that there is no gross hereditary defect in the common stock

Since the health and happiness of the United States depend so much upon the predominance of the physically mentally and emotionally fit stock the state may well inquire into the relative fertility of the most effective and *the least* effective strains At this time throughout civilized countries, and particularly in America through voluntary limitation of the size of families the most successful stock is not reproducing itself in anything like the proportion of the less successful stock The sons of Harvard University have only about 0 8 of a son on the average, while the daughters of Wellesley have even a smaller proportion of daughters Into a population which is strictly not reproducing itself there has entered a strong propaganda for the dissemination of birth control' information Were it possible through the spread of such information to diminish the *relatively greater fertility of the less effective stock, the propa*ganda would be biologically advantageous The birth controllist however early found that the less effective and thrifty stratum did not respond to the propaganda for reduction in size of families for the parents in such stratum each child was regarded as an economic asset The birth controllists there-

with agglutinogen A in the blood and its known parent belongs to the group which produces agglutinogen B then it must be that the other parent belongs to the group which produces agglutinogen A or to the group that produces the two agglutinogens A and B Similarly a child that produces agglutinogen B and whose known parent produces only agglutinogen A or produces no agglutinogen must have had as its other parent one belonging to the group of B, or A B The table describing all the possibilities for the unknown parent of disputed children with particular blood groups is given in treatises treating of the blood groups of which may be mentioned that of L H Snyder

The facts of heredity may be advantageously used in other matters of social importance such as giving advice in respect to the choice of a profession Specifically we may answer the question whether a given boy would probably succeed as a physician or surgeon It is necessary before such advice can be given to consider the distribution in the family tree of high degree of success in the given profession We do not know just how the different traits which are responsible for success in a given profession are inherited We do know however that in some cases as in medicine and surgery striking cases of outstanding success in three four or more generations are known This would seem to suggest that there is at least one essential factor in such success which is inherited as a dominant trait

To the psychiatrist a knowledge of family history of patients is of vast importance and this fact is so generally known that family histories are now regularly taken in the best developed institutions The late Dr E E Southard of Boston stated that he would hardly diagnose with confidence a case of manic depressive insanity whose family history showed no other individuals who might fall into the same category It is important however that the psychiatrist should not depend for knowledge of the family merely upon testimony of relatives who accompany the patient to the hospital since for social reasons such relatives tend to minimize the importance of the genetical factor and to cover up striking cases of similar defect in the family Accordingly many institutions find it advantageous to employ field workers who can be sent to the homes from which the patients come in order to make first hand observations and inquiries concerning the traits of other members of the family

Instead as is so often done of regarding heredity as a dour doctrine and one whose conclusions are fatalistic and opposed to the program of human improvement that is being promoted by sociologists and physicians it were better to look upon heredity as a power for social regeneration of the first importance Every farmer recognizes the incalculable value of heredity in the production of his best stocks He controls his matings with the greatest care since he knows that the value of the next generation will depend upon such matings It is to be hoped that in time in civilized countries it will be ap-

Recognition of the fact of heredity does not render unnecessary efforts that have been made toward education and moral and religious culture Even plants to yield their best fruit, must be cultivated and the innate good traits of children may be repressed by a "bad' environment Eugenics, however, teaches that it is as futile to try to train the feeble minded boy to be a scholar as it is to try by cultivation to make a golden bantam variety of corn into a giant Our efforts toward education will be more effective when we recognize first that children are all different, and when we seek, secondly, to develop to the utmost those germs of desirable traits that they possess, and thirdly, to repress undesirable tendencies So also in matters of health the physician must recognize that all of his patients are different, and he must urge therefore, different hygienic training in accordance with individual needs It is sometimes said that eugenics is a medical matter, and so it is indeed, but it is also a social matter of the highest import It is for physicians and those interested in social welfare and social development to unite in applying the principles of eugenics to the advancement of the State

The facts of heredity may be well called upon to aid in certain legal procedures especially in determination of disputed paternity Insofar as the laws of inheritance of traits have become definitely established, they can be utilized to advantage in such disputed cases For example the established principle that two parents, both of whom produce no melanic pigment in their irides can have only children with the same trait may be used to decide matters of disputed parentage or to decide whether a given claimant for an estate on the ground of relationship to his alleged parents has a just claim Valuable in this connection is the fact of inheritance of the factors that cause iso-agglutination of the blood It appears that the red blood cells of many persons produce an enzyme called agglutinogen' which leads to the production in the serum of the blood of corresponding "agglutinins The commonest of the agglutinogens that are known are designated as A, B, and the corresponding agglutinins in the serum are designated as a b If now the blood of a person who carries in the cells agglutinogen A be mixed with the serum from a person with agglutinogen B and therefore with the agglutinin b, then the blood cells derived from this individual tend to clump in the drop On this account it is important, in the case of blood transfusions to secure a donor of the same blood group as the person into whose veins the blood is to be injected, otherwise agglutination will occur and through consequent blocking of the blood vessels serious effects and even death may follow Besides the two types of persons who produce agglutinogens A or B there is a third type that produces both agglutinogens A and B and corresponding agglutinins a and b Finally, there is a fourth group which produces no agglutinogens Such persons can receive infusion with impunity Now, if a given child belongs to the group

CHAPTER XII-A

ALBINISM

By FREDERICK R TAYLOR

TABLE OF CONTENTS

Synonyms — Albinismus congenital leukopathia congenital leukoderma congenital leukasmus congenital achromia dyschroia moon eyes children of the sun (Guatemala)

Definition — Albinism is a congenital condition which in its complete form is characterized by a total lack of the melanin group of pigments in the body its striking features in man being a lack of pigment in the skin hair and eyes with resulting photophobia nystagmus high grade refractive errors and extreme susceptibility of the skin to strong sunlight and other potent sources of ultra violet radiation Other body pigments not included in the melanin group such as lipochromes urochromes blood and bile pigments etc are present Incomplete and partial forms of albinism occur Albinism is found widely distributed throughout the animal kingdom and an analagous condition due to absence of plant pigments occurs in the vegetable world

HISTORY

While albinism has doubtless existed from a very early period in the life of man references to it in ancient literature seem surprisingly scant for such a striking condition Lagleyze of Buenos Aires who probably has given the most exhaustive discussion of the subject in the literature states that a passage in the Elder Pliny s writings seems to indicate

preciated that the future of the country depends especially on the quality of the germ cells that are being transmitted to future generations If these germ cells determine the development of individuals of the highest quality, they become invaluable One sees vast sums, amounting to even hundreds of thousands of dollars, that are spent for particular animals, such as the horse or the bull, to be used for breeding purposes The money is not spent for muscle or bone, but for the literally microscopic enzymes that are carried in the germ cells If all the enzymes that were used in reproduction should be brought together, they would still be beyond the limits of visibility or of weighing For the possession of such invisible materials persons are willing to stake a fortune If the enzymes for successful race horses, or for great milk producing cows are of such value, how much more should we treasure the germ plasm in our population that is responsible for the most valuable social qualities

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recessive characteristic Mudge Jablonski Pardo Castello and Musser among others definitely subscribe to this view Musser explains the relative rarity of albinism by the fact that the health of albinos usually is poor and they often die without propagating Swab records the case of a white man who married a negress they had a black daughter when *she became 15 years old her father had incestuous relations with her and* an idiot albino resulted Wakefield and Dellinger have described a pair of albino identical twins of negro parentage A view formerly held that albinism represents an atavistic reversion to a special race of albinos has been practically abandoned Consanguinity in the parents seems to predispose somewhat to albinism Lagleyze studied 27 albinos in 13 families among these 13 albinos in 5 families had consanguineous parents The 27 comprised the total number of albinos he had seen among 30 000 patients In no case did an albino child have an albino parent In addition to his own cases Lagleyze studied the data on 48 families in the literature with 290 children 104 of whom were albinos In 10 of these families the parents were stated to be consanguineous without mention of albinotic heredity in 7 albinism was reported in collateral antecedents in 5 there was no mention of familial factors

Garrod suggests three possibilities to explain the pathogenesis of albinism as follows (1) a structural peculiarity of the cells which renders them incapable of pigmentation (2) an absence of the material from which melanin is formed (3) the lack of a specific enzyme which brings about the formation of melanin

A number of observations seem to support the last hypothesis at the expense of the first two among which are the following

Mudge noted that in albino rats immersion in formalin turned the hairs a vivid yellow Subsequent immersion in hydrogen peroxide turned them a brownish color He believes that this proves the presence of a chromogen and indicates the absence of a ferment in albinism that normally converts the chromogen into pigment He quotes Cuenot as suggesting that the pigmentation of mammalian hair is due to the interaction of a chromogen and a ferment He also cites the work of Miss Durham who extracted in water from the skins of young rodents a material which when incubated with tyrosin to which a small quantity of ferrous sulphate had been added as an activator threw down a pigment of the same color as that of the hair growing out of that particular portion of *skin* Mudge also notes that breeding experiments show that albinos carry some pigment factors Mudge s findings were confirmed by Sollas Schultz showed that a piece of albinotic rabbit skin containing growing hair when kept for from seven to twelve hours under certain conditions of

that he had seen a case of albinism and that Hernando Cortes is said to have mentioned albinos at the court of Montezuma There seems to have been little general scientific interest in albinism, however before the 18th century when many accounts of the condition by various travelers appeared notably the early explorers in Africa who reported albinism in Guinea, Algeria Madagascar and along the Congo Lagleyze tells us that in 1704 Wafer described albinos in Panama Apparently albinism was not generally recognized in the white race until very recent times for Lagleyze says that in 1774 DePaul stated that albinism did not exist in Europe and that it was found only within ten degrees of the equator However ten years later Blumenbach described some albinos at Chamonix in the Alps and apparently was the first to attribute the red light in the pupil and the apparent color of the iris to their true cause During the past century albinism has been reported in all races from practically all parts of the world though its frequency varies greatly in different localities

Of special interest to the ethnologist are the varying attitudes of primitive peoples towards albinos Often persecuted or killed albinos have been objects of veneration in some places especially where they are rare Certain negro tribes represent the devil as having a white skin In Guinea albinos have been considered sacred and invulnerable in Senegambia as possessed of evil spirits in Uganda they were wondered at as curiosities and kept about the kings According to Lagleyze on the island of Parrot in the mouth of the Calabar River in West Africa the natives sacrificed an albino child to the god of the whites when no European merchant ship had called in a long time

Among many interesting primitive beliefs regarding albinos may be noted the following that they are born of women impregnated by gorillas that they are born of women who while asleep in the forest were impregnated by meteors that the morning star is the father of all albinos that the devil is their real father

Lagleyze quotes Dubois as stating that in certain parts of India the natives used to draw and quarter albinos and throw their bodies on manure piles or to ferocious beasts

Etiology and Pathogenesis

Little is known of the etiology of albinism other than that it is a congenital defect in the mechanism which gives rise to the melanin group of pigments in the body For many years a battle raged over the question of the etiologic significance of heredity many authorities denying its influence but the weight of opinion today regards albinism as a Mendelian

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moisture and oxygen at a temperature of from 30° to 36° C would develop a strong melanin pigment at the hair roots By a similar method the iris of a newborn albino rabbit became pigmented

Garrod calls attention to some interesting findings of several investigators as follows Halliburton Brodie and Pickering noted that intravenous injections of nucleoproteins in albino animals failed to produce such clotting as in pigmented ones Mudge found that all albino rabbits were not alike in this respect but that in general more nucleoprotein must be injected into albino animals to cause death from intravascular clotting than into similar pigmented controls Pickering also noted that the Norway hare in its winter coat reacts like an albino when injected with nucleoprotein whereas in summer it reacts like any other pigmented animal Bickel and Tasawa found that exposure for several weeks to a bright light increased the red cell count in pigmented animals but did not do so to any appreciable degree in albinos

Symptomatology

Complete albinism presents the following symptoms and physical signs The skin is milky white and looks thin and delicate The superficial blood vessels are conspicuous The hair is fine and almost white of a very pale silvery flax color The irides are untinted and appear red pink or violet according to the intensity of the light by which they are seen looking red in a very strong light and violet in a very subdued one There is a red pupil reflex due to the lack of pigmentation within the eyes which resemble those of a white rabbit Because of the lack of protective pigment in the eyes photophobia is marked and nystagmus is an almost constant finding The latter usually develops in early infancy though occasionally it is present at birth As a rule it is horizontal rapid and of wide excursion though rotary and mixed forms have been described Lagleyze explains the nystagmus as an effort of the eyes to escape from the irritating light The nasal side of the eye being more shaded than the temporal the eyes move back and forth in an effort to relieve the points of momentary maximum irritation

The extreme photophobia develops a characteristic attitude and facies in which the head is bent forward the eyes are kept partially closed there is a constant frown and in a strong light the patient will nearly always shield his eyes with a hand as with a vizor unless they are suitably protected The pressure on the eyeballs from the contracting muscles is considerable and this soon gives rise to a high degree of refractive error, which may be hyperopic or myopic and is always com

plicated by a very marked astigmatism Chronic blepharitis naturally is the rule In addition the visual acuity becomes markedly reduced and usually is found to be from 1/6 to 1/10 of the normal This is a true amblyopia which remains after refractive correction All these phenomena tend to make the albino look abnormally old Often the optic discs appear about the same color as the rest of the eyegrounds which are of course pale and can be found only by locating the entrance and exit of the retinal vessels In other cases they may appear a deep red or an ashy gray Color vision and the visual fields are unaffected Laqueyze has noted persistence of the pupillary membrane in a few albinos and states that he has not seen it in non albinos Concomitant strabismus often occurs in albinism Shaad noted that albinos adapt their vision to relative darkness less rapidly than normal persons but their vision became more sensitive in the dark after 10 minutes than that of normal controls and remained so throughout the remainder of a 30 minute test The name moon eyes sometimes applied to albinos is based on the fact that they can see better by moonlight than by bright daylight

Intelligence is unaffected by albinism All grades of intelligence from idiocy to brilliance have been noted as in non albinos

The skin will not tan in the sun and is very susceptible to sunburn and irritation from other types of ultra violet radiation Garrod states that melanotic tumors do not occur in the albino and that there is no record of an albino with Addison s disease The hyperpigmented areas usual in pregnancy do not appear in albino women Hewer reports three cases of multiple epitheliomata in Egyptian albinos which he considers due to the action of the sun s rays on the unpigmented skin

A number of associated anomalies have been noted in individual albinos but these probably are to be looked on as coincidental rather than as bearing any relation to the albinism The writer has studied a case of albinism in a young woman a virgin who had in addition to a severe dysmenorrhea a practically complete congenital absence of the muscles of the pelvic floor the vaginorectal septum being almost as thin as paper

Albinism may be classified as *complete incomplete* and *partial* The *complete* form has been discussed *Incomplete albinism* is a condition in which there is a general deficiency but not complete absence of the melanin pigments There are all grades of this with corresponding degrees of severity of symptoms

In partial albinism there are contrasting albinotic and normal areas throughout the body If an eye is in an albinotic area it will be affected otherwise it will not Only a portion of an eye may be involved Hair

growing out of albinotic areas is devoid of pigment that growing out of normal areas has the normal color A number of instances of red haired albinos have been recorded Garrod states that the pigment may be present in the eyes alone in which case the other ocular phenomena of albinism are likely to be absent Squire reported the case of an albino whose entire skin and hair system were pigmentless but whose eyes were dark blue who had no photophobia but who did have horizontal nystag mus so that he had difficulty in reading though his visual acuity was normal

A piebald appearance often occurs in partial albinism and probably represents a mosaic inheritance Pardo Castello regarded all such cases as probably achromic nevi Traub however has given us a differential criterion viz that piebald albinotic areas become hyperemic on friction with ice whereas achromic nevi do not Firth has made the interesting observation that individual red hairs from the scalp of a black haired African showed the same characters as the hairs do in red haired albinos

Diagnosis

Diagnosis of albinism usually is obvious on inspection Occasionally partial albinism may have to be differentiated from achromic nevi by *Traub s method as described above Vitiligo is distinguished* from partial albinism by the fact that it is an acquired condition whereas partial albinism is congenital

Prognosis and Treatment

Garrod states that albinos occasionally may acquire pigmentation in childhood or early life The condition usually is permanent, however Poor health due to the eyestrain and to various other associated conditions often occurs so that the life expectancy of an albino probably is less than that of a normal person of the same age

Treatment is largely a matter for the ophthalmologist who must be consulted for protection of the eyes from light and for proper refraction The piebald cases may benefit from dermatologic advice as certain stains have been devised for use on the pigmentless areas for cosmetic purposes In such cases the recently introduced ' Covermark also might prove helpful Strong light should be avoided and special precautions taken against sunburn Exposure of the body to other forms of potent ultra violet radiation also is contraindicated

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CHAPTER XIII

ADOLESCENCE

By WILLIAM PALMER LUCAS

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Introduction

The adolescent period represents the second most rapid period of growth in a child's development From the anatomical standpoint this period does not represent as rapid a growth as the period of infancy but the significance of its anatomical psychological and physiological development is greater than at any other period of growth During this period certain finalities along the lines referred to are definitely established At the same time the period covered by adolescence is a fluid one the finalities established when adult life is reached have passed through various phases of development The very character of this period of adolescence therefore demands a most careful analysis of the different stages of the development But more than that it demands also of the study of medicine a more fluid attitude toward this field and a wider knowledge of the social experience through which a child passes during the stage of development A sympathetic appreciation of the child's world is absolutely necessary if the changing phases of this period are to be intelligently related to the whole field of medicine The study of

the adolescent period is therefore a study of constant changes and the relation of these changes to each other and to the whole development is the effort attempted here

Growth Changes of the Adolescent Period

General Body Growth

The accepted opinions on this subject recognize the so called time element which must be considered i e the fact that growth as it takes place at any given period is a variable Growth proceeds in curves rather than in straight lines during any period and the very waves of the curves vary in height and width Thus during the period of adolescence growth must be considered from the particular part under observation rather than from the general standpoint Space permits of discussing only the main points of growth during this period The size of the skull remains practically the same any slight change being relative to the growth of other parts of the bony structure such as the increased lengthening of the face by the growth of the jaw bone

A marked difference takes place in the chest during the adolescent period the growth takes place laterally and we have increased width in the chest cavities rather than any marked increase in depth The long bones of the body increase rapidly in growth and here the growth curves vary at different times during the period and in the two sexes differences in the time element have been noted The final attachment of the epiphyses that have not already ossified takes place during this period The final rounding out of the muscular system is the 'normal" muscle limit of this period This long bone and muscle development of the adolescent period bears an immediate relation to several of the most common characteristics of the so called awkward age ' When the bones grow more rapidly than the muscles we often have the 'growing pains of adolescence as the physical result Also this rapid growth of bone without the muscular development to uphold the bony structure results in poor posture for the child with far reaching results of such abnormality

When the muscles grow faster than the bones the joints are loose and this often accounts for the ungainly habits of the adolescent child The clumsiness noted in the child whose earlier muscular skill had been marked is often caused by the rapid growth of the large muscles employed in the finer more detailed use say of one s hands Take the emphasis placed upon the piano lessons of the small child The finer muscles are developed then—if this were not so they would lose their chance for development during the adolescent period as that period is

mainly devoted to the development of the large fundamental muscles The end of the adolescent period has in the main usually established the final bony structures Both the shoulder and pelvic girdles in boys and girls develop rapidly during the period The pelvic development in both male and female is the most clearly defined in the adolescent period the female pelvis becoming broader horizontally than the male and parallels in its development the growth of the generative organs The male pelvis becomes more fixed than the female as the complete ossification of the female pelvis is deferred to a later period This is a most important point in the problems of attending maternity

Finally within certain broad limits the appearance and development of metacarpal bones is of value in estimating the different periods of development This metacarpal development however cannot be used as an absolute gauge either physiologically or chronologically for any definite age The rapid increase in height which includes not only the more rapid development of the extremities but also the slower but gradual lengthening of the trunk is the essential index of development during the adolescent period The child should be taught to be proud of his height and not allowed to develop bad posture which only increases his awkwardness and often leads to permanent deformities such as scoliosis

Growth of the Heart

The heart develops rapidly during the period of adolescence The increase in size and strength is marked the volume of the heart increasing from 160 to 225 cubic centimeters This is not only a growth in the size of the contractile fibers but also in the number of fibers Before puberty the blood vessels are large and the heart small With the increase in the size of the heart this relation changes The more rapid this adjustment between heart and arteries the sooner and more complete is the adolescent development The general tendency during this period is for the rate of the heart to diminish and the strength of the individual contraction of the heart to increase but there are many unaccountable variations in the heart rate and the forces of the cardiac impulse These variations cause at times pronounced palpitation at other times marked slowing down of the heart rate This often causes alarm in the child awakening so to speak a consciousness of his heart which he does not understand These symptoms are very disquieting and often recur without an apparent cause It is probably more exaggerated on over exertion such as muscle or nervous fatigue This alarm should be sympathetically dealt with by a simple explanation of this growth to the child and a carefully planned regimen which avoids the state of over fatigue of any kind The disproportion between the general develop

ment and the development of the heart, which often accounts for these symptoms can be demonstrated not only by physical examination but most graphically by radiography

Growth of the Lungs

The vital capacity increases with the development of the chest This development as in the development of the heart proceeds in curves rather than straight lines, and nothing affects its development more than proper breathing and correct posture There has been a great deal said about this being the period of marked change in the breathing of the sexes the boy maintains the more normal and abdominal breathing the girl develops thoracic breathing This is not a true sex difference but is artificial and due to the radical change in dress between the sexes as has been clearly demonstrated by Mosher (1) During the adolescent period tuberculous affections of early childhood are likely to become active processes The early infection of the bronchial glands extends to the lungs during this period of the direction of all surplus energy to growth Hygiene and careful supervision of those who have had gland infection in earlier childhood is most important at this time to prevent this pulmonary extension Excessive fatigue and acute infections are most important to avoid

Growth of the Brain

The adolescent period is the most important one in the differentiation of the brain At this time there are more active cells The size of the brain and weight of the brain have reached their maximum in the pre adolescent period but adolescence marks the intensification of the differentiation of the fibers which represent the higher intellectual powers The nervous system gives a clear illustration of regular and orderly growth The higher centers depend on their development upon the growth of the lower centers This development of the higher centers progresses rapidly during the adolescent period connecting the sensory and motor areas This growth of association fibers is apparently stimulated by the appearance of our higher intellectual powers During the adolescent period there is undoubtedly an increased stimulation in new centers These centers are not limited to sensory or motor aspects but undoubtedly have to do with the higher centers of volition and will The inter reaction of different centers causes development and growth of other centers so that we have a number of different periods of growth as it is true that certain fibers become medullated far earlier than others During the adolescent period new interests and cravings appear and undoubtedly are related to the maturing of certain association centers

Growth of the Larynx

The larynx grows rapidly at adolescence with quite a marked sex difference the male growing larger than the female All the cartilages are enlarged and the thyroid cartilage in the male becomes quite prominent and the glottis nearly doubles in length This development of the larynx includes the development of the vocal cords which lengthen and thicken accounting thus for the change in voice especially in boys during this period A boy s voice commonly breaks at this time and often becomes a full octave lower

Growth of the Reproductive Organs

The first indication of the growth of these organs is found in the development of secondary sexual characteristics Hair begins to appear in the pubic regions and the armpits of both boys and girls In boys there is a more marked increase in hair on the face chest abdomen as well as all over the body In girls there is a marked rounding out of the hips and the development of the breasts The reproductive organs themselves begin to develop in size The penis and testes of boys show marked change in size as do the uterus and vagina in girls

PHYSIOLOGICAL DEVELOPMENT AND CHANGES

The *foregoing general discussion of growth leads naturally to the* consideration of the effect of growth upon the function of the organs of the body and the resultant physiological changes At the time of the beginning of the development of the sex organs we have the first fundamental appearance of the physiological activity of the gonad system or sex glands This development is one of the most complex processes taking place in the body because upon it is based the differentiation of the sexes and the power of normal reproduction in both The development of the gonad system is intimately associated with the normal functioning of other internal glands Any disturbance in the pituitary glands usually affects the normal development of the sex glands Changes in the adrenal and thyroid glands also affect the normal functioning of the reproductive glands

Closely paralleling the development of the internal secretions come the external signs of sex functioning which at the beginning often cause great mental and nervous suffering In boys the appearance of nocturnal seminal emission is not at all regular recurring at first at infrequent intervals and normally at the height of puberty not oftener than once in ten days or two weeks This emission is often accompanied by

dreams The semen is composed of a thick gelatinous secretion containing many active spermatozoa Menstruation in girls occurs with great regularity, the normal periodicity being twenty-four days The duration of the flow varies in normal limit from two to five days Under conditions of poor hygiene, both physical and mental, the menstrual function is very often disturbed and this disturbance often produces the common pathological condition of amenorrhea and dysmenorrhea In a few instances these conditions are undoubtedly due to derangement in the internal gland secretion, but by far the majority are due to improper hygiene

Menstruation is undoubtedly influenced by the internal secretion of the ovaries The thymus the posterior lobe of the pituitary and the thyroid are also supposed to play a part in menstruation There is undoubtedly a relation between the mammary glands which become enlarged immediately before the menstrual period During menstruation the uterus is markedly hyperemic and the flow of blood is the result of this normal condition This blood contains varying numbers of endothelial cells from the uterus and epithelial cells from the vaginal tract Changes in the skin occur constantly during this period In girls the pigmentation is most pronounced in the areola of the nipple The decided change in the complexion of both boys and girls is marked at this time The sebaceous glands enlarge and become more easily infected and are responsible for the frequency of acne during adolescence Blackheads are very common during this period caused by the growth of the sebaceous glands and the pigmentation Connected with the skin changes are the presence of characteristic body odors, which are more pronounced in girls during the menstrual period Perspiration increases in both boys and girls The activity of the salivary glands increases during this period The spitting contests of the small boys are familiar to all During the adolescent period the physiological changes in the organs of sense are on the whole slight Sight and hearing are not affected Smell and taste are slightly accentuated The craving for sweets is a common symptom The tactile sense may be increased or diminished

Psychological Development and Changes

Adolescence is the period of great awakening and change both mentally and morally The child passes from the gang stage to the stage of a larger group society in general He becomes more conscious of himself as an individual and that consciousness demands his own relation to others as well as to his environment The desire to count as one and a part of the whole slowly overshadows the former contentment in act

ing merely in the gang spirit This change cannot be tabulated It is even more fluid than the physical change The only wise method is the constant study of each phase as it presents itself For the first time consciousness of dress appears in both boys and girls Anything that seems to call attention to oneself is the most sought after a tie of gay colors a bizarre ornament worn at an unusual angle all the many ways in which the individual may be marked by his kind On the other hand there may be periods of absolute personal neglect arising from the same individual awakening and marking a stronger development to be in a group yet not of it is an old standard of moral strength

The actual mental caliber of boys and girls at this period may be equally baffling Sometimes it is marked by precociousness in their mental processes They may show a great power of assimilation in a subject that interests them again they may be absolutely indifferent o any mental achievement and for the time being have lost interest in anything and everything that has to do with their mental development These mental states are usually closely associated with their physical development When their physical development seems to be progressing most rapidly the mental activity seems to be at a standstill Often the strength of the child is entirely ab orbed by the physical growth At other times when the physical development progresses slowly the mental activity may develop very rapidly Again there may be a rapid and even development of both the physical and mental powers or there may be a slow and even development of both the physical and mental powers and lastly that most baffling of all phases when both the mental and physical developments seem to be marking time These unevennesses are marked mentally and emotionally in various ways

Sex attraction now manifests itself and often begins with a strong devotion between members of the same sex Boys have their boy heroes of their own age and older Girls are more apt to be attracted by older women especially their teachers Adolescence is often marked by vivid religious emotions and aspirations utterly unfounded likes and dislikes periods of uncontrolled temper periods of equally unreasonable spells of contrition periods of great excitement and high spirits and again periods of deep depression Taste in food as well as dress suffers from the uneven developments of this period All these manifestations differ in degree and intensity throughout the whole period of adolescence and there seem to be no consistency in sequence in any two individuals Therefore the understanding and relative importance of these changes necessitates a careful study of each child The period is marked by greater variations within the normal than any other period of human development

In spite of all this ebb and flow this varied expression of adolescent contrasts and inconsistencies in the relationship between the mental and physical development certain definite mental finalities are steadily being approached At the end of adolescence the power to reason has become stabilized and ready for its mature development The will power most unstable during adolescence if normal in development becomes more fixed and ready to build upon The character development during adolescence is but a continuation and molding so to speak of processes begun in the very earliest adaptation of a child to its environment During the adolescent period the same "fluid" conditions exist in the moral adjustments as in the physical and mental development We often find that a child during this period of adolescent variation develops weak or vicious traits which unless properly and sympathetically guided might become stabilized If so guided the child when adolescence is completed emerges with the moral finalities that were established long before the adolescent period began At the same time the child entering the adolescent period with the wrong moral concepts has in the very nature of the period itself its instability and variation a new chance to develop the right moral valuation Such moral development during adolescence is closely related to the development of the mental powers such as the reason and the will For reasons such as these, the strongest emphasis must be placed upon the care and guidance of children through this period as it is the last opportunity for the molding of character While not as important as the earlier stage, still it is the last opportunity for permanently affecting character formation Radical changes of character after the completion of adolescence are rare and are usually the result of great or disturbing elements in life such as religious conversion or exposure to tremendous emotional experiences great joy fear or tragedy as the war has demonstrated

The Defects of Adolescence

Such a period marked deeply as it is by constant change growth and development along physical mental and psychical lines is naturally marked by defects of great gravity These defects naturally fall into two groups—the defects of heredity and acquired defects Defects of heredity again fall into the two main groups of those inheriting mental defects and those inheriting moral defects The mental defects which appear first during adolescence are mainly the moron group These individuals form a great part of our adolescent juvenile offenders especially among girls The increased instability of the period plus the weak mentality minus a good environment leads usually to the breaking of some

social law in these cases In girls it is more often a sex offense in which case they are more unmoral than immoral having been used by normal people who should be the real offenders against the law As to boys of the moron group we find them in the same status being used by brighter more normal individuals as tools and the common offenses are larceny truancy and depredations of various sorts The moron it must be remembered is the individual whose maximum intelligence equals the normal intelligence of twelve years

During the unstable period of adolescence the moron can be trained into certain habits of life and work that will make him often economically independent This can be accomplished by vocational training along manual lines under careful supervision Nor does this mean constant institutional care By special classes in the public schools combined with constant careful follow up work in the homes many of these individuals can be kept out of trouble and can constructively use the limited abilities they possess This type of care is possible but it is only possible with community understanding and cooperation between school family and the follow up workers The majority of morons who go wrong during the adolescent period do so from a lack of this cooperative effort and a lack of understanding of a child s limitations The stress and storm of the adolescent period is much harder on the moron group than upon the normal child because they lack the development of the higher mental traits reason will power and judgment which come to the normal child during that period The moron s maximum intelligence of twelve years may not be reached until the later years of adolescence which makes the problem very much more difficult The adolescent changes have to be met without the stabilizing effect of mental development On the other hand many of the moron group do not seem to experience the stress of the adolescent period but on account of their lack of mental development are just as easily led astray Many of these children cannot be cared for successfully in communities where general understanding and cooperation are lacking and as such communities are as yet in the vast majority in the world the institution becomes a necessity for the care of the moron The type of institution however should be one which embodies all that outside care might in special instances accomplish The old idea of merely shutting such children away from the world has passed forever and the new institution has as its goal the final placing of the moron in society again so stabilized and trained by habit and education fitted to his powers that he can be a self supporting and self respecting member of the group This would always necessitate a certain amount of intelligent supervision varying with the demands required of the individual and the changing environment Friendly advice from the

modern trained medical social worker should always be available to this group in order that the individual may be able to make his adjustments to new demands without a loss of the training he has had

Another group which suffers keenly during the adolescent period is that composed of children whose mentality is not below normal but who suffer from lack of moral stamina These children are much more difficult to detect because their intelligence is normal They show usually a total lack of the social sense no perception of right and wrong and from this group come many of our criminal class and the worst offenders against sex laws The understanding and management of this group is much more difficult than that of the moron and the success of training and supervision is markedly less because their intelligence gives them an advantage If at early periods some decided bent or aptitude can be discovered and the training and supervision related to it most carefully and intelligently applied the chances of success are much greater

A third group of defectives which appears usually during the adolescent period is that of so called constitutional psychopaths These individuals are of varying types their principal defect being their inability to adapt themselves to the normal environment Many in this class have what is recognized as a hereditary nervous background (diathesis) which shows itself in the constant impulsive basis from which they act We find in this group all our cranks kleptomaniacs pyromaniacs, agitators and all the impulsive types that make up our grave social problems The keen intelligence which often marks these impulsive psychopaths makes them most difficult to treat with the intelligence they demand During adolescence these types first reveal themselves and that period should be most carefully studied by students of medicine In the past there has been little appreciation by the medical profession of the importance of such manifestations during adolescence But of late such intensive studies as have been carried on by Healy ([2]) and by the best modern psychopathic hospitals juvenile clinics and juvenile courts have brought to the attention of the medical profession a vast amount of material that shows the importance of the understanding of the heredity and environment of these cases

The fundamental aspect to be stressed in handling these cases is to make every attempt during the plastic period of adolescence to force upon these individuals the realization of their own condition In this is a surer hope of solution for them Psychoanalysis if used at all should be used not so much in the Freudian sense of establishing all lines of relation of abnormal traits to sexual development as in the analysis of the individual s own life so that he will understand his own weaknesses and handicaps In modern social psychology we have a better

means of stimulating the child to an appreciation of the development of his instincts and so helping him to gain a more stable control over his defective impulsive bases

Another group of defectives are those suffering from language and speech defects which may or may not appear before adolescence but which do often appear and usually meet medical attention first during this period Children with these defects are often normal in every other respect These defects may be permanent or temporary and the importance of understanding them is in order to be able to classify them so that the training of these children may proceed along the lines in which they are normal and in this way to diminish their handicap as much as possible

Other types are those defective in number work This often causes a classification of these children as feeble minded when the defect is limited to this one faculty Stammering and similar speech defects which appear during the adolescent period in the nervous or timid child have a definite neuromuscular and mental or psychological basis These conditions may be begun through imitation a sensitive child often acquires an actual speech defect from contact with another suffering from such a defect Such defects may also be acquired after a definite fright or shock of any kind to the nervous system Of course this acquisition of such defects may appear at any age but before the completion of adolescence they must be handled if possible as delay in treatment increases the chance of permanency The treatment should be carried out by one acquainted with the psychology of childhood as well as the mechanics of voice production and control Many of these speech and language defects are hereditary many are acquired and some have the double basis

Diseases of Adolescence

This period is marked by the development of definite psychoses mainly those of mania and melancholia These states often have an hereditary basis but are usually brought into evidence by the awakening of the sexual functions The state of mania is characterized by periods of intense excitement uncontrolled temper followed by periods of great fatigue Sometimes intense jealousy great selfishness sharp depression are manifested The state of melancholia is expressed by constant depression maintained sometimes over long periods While there are intervals of normality and cheerfulness depression is the more constant symptom

The treatment of these states requires as early a recognition as possible and a careful analysis of the causes either real or imaginary that

have brought on these states The removal of the causes and the placing of the child in the best possible environment which will prevent a recurrence of the cause is the best line of treatment to be followed In the more severe cases institutional care is necessary, but the outcome of these cases is not good because they often become chronic or fall into such bad *nutritional condition that they often die of some intercurrent disease* The adjustment of these cases to everyday life is one of the most hopeful fields of modern psychiatry Careful study of the individual case with the necessary change of environment and the personal follow up work of a trained psychiatrist and social worker bids fair to be the best solution possible for these cases

A common mental condition of adolescence is *dementia praecox* On account of the stress of rapid change of this period dementia praecox with its gradual decay of mental faculties is very likely to appear in the early and confusional states At that stage it is often difficult to differentiate the state from an exaggerated adolescent condition of instability which corrects itself In the most common type of dementia praecox the hebephrenic type are found states of increased excitement alternating with foolish laughter and silly speech, an exaggerated impulse to be doing something which is only evidenced by perfectly aimless actions which accomplish nothing These conditions may persist for a long time without any evident increase in the mental decay, but in general these states terminate in extreme mental weakness followed by the complete destruction of the mind Other forms of dementia praecox may begin at puberty such as the catatonic form in which states of depression are followed by alternating periods of stupor and excitement shown by varied motor spasms or retardations *Paralytic dementia* also has its beginnings frequently at the period of adolescence All these states when actively manifested are best handled in an institution

Syphilis is the underlying cause of many of the mental deteriorations during the adolescent period Hereditary syphilis is sometimes retarded and without having shown any previous manifestations either in the physical or mental development of the child develops very rapidly during puberty Especially is this true at the time of the development of the sexual functions and manifests itself by rapid mental deterioration or by the development of juvenile tabes Active treatment with mercury and salvarsan or neosalvarsan begun early may be able to check the condition but these conditions more often continue to rapid disintegration both mentally and physically Such cases usually die of some intercurrent infection

Because of the fundamental change in the brain and central nervous system and marked physiological changes *epilepsy* reaches its most

marked development during adolescence Instead of the hoped for cessation of symptoms they are usually exaggerated during this period When *chorea* appears first at adolescence it is marked by greater severity and longer periods of duration The characteristic involuntary movements are usually accompanied by irritability absent mindedness and slight mental weakness

Changes in the composition of the blood during adolescence often take place especially the anemias which are marked by pallor and great languor In boys this usually takes the form of simple secondary anemia *due to the effects of malnutrition or previous infection* *During* adolescence this secondary anemia may become quite pronounced on account of the increased demands of growth and the disturbances caused by the development of internal glandular secretions on the lymphatic system In girls these anemias often take the exaggerated form of *chlorosis* in which there is a definite disturbance of lymph formation The red cells are not able to carry their normal proportion of hemoglobin so that the characteristic finding of this condition is a very marked reduction in the hemoglobin without a corresponding reduction in the red cells In severe cases poikilocytes and normoblasts make their appearance Connected with these blood findings are marked lassitude and fatigue which chlorotic girls suffer from and also distinct nervous phenomena such as headache vertigo insomnia and general nervous instability These conditions are often accompanied by hemic murmurs of the heart and change in the blood pressure Their treatment requires careful regulation of diet and regime based upon a study of their previous condition making sure that the cause is neither syphilis nor tuberculosis Iron in most instances has a very definite effect upon these anemias

The endocrine glands exert a powerful influence upon adolescent development of both girls and boys not only on the development of the sex organs and functions but also upon the secondary sexual characteristics The functional activity of the sex organs depends upon the harmonious action of the endocrine system upon the efficient and normal action of this system It is not sufficient to have merely the sex glands develop The development of the sex glands is so intimately connected with the development of the thyroid and pituitary glands that the two must progress in parallel lines We know that the thymus gland begins to disappear about the time of puberty Whether this disappearance of the internal secretion of the thymus causes the beginning of the development of the gonad system with its internal secretion or whether the appearance at this time of the internal secretion of the gonads causes the disappearance of the thymus gland is not known The reaction is probably mutual Any change in the development of the thyroid or the

pituitary causing an insufficiency of its internal gland secretion retards the development of the generative organs A tumor in the pituitary will cause infantilism Most of the cases seen during adolescence of retarded or abnormal growth are due to a combination of defects in the endocrine system usually a polyglandular one The thyroid gland during the adolescent period is very prone to enlarge, especially in girls Marine ([2]) in his studies, "Thyroid in School Children," found it four times as often in girls as in boys This increased tendency to thyroidism during adolescence has a definite effect upon the development of generative organs The period of nervous instability is markedly increased by this tendency It seems fair to assume that the instability and the varying phases of great fatigue and excitement are caused by the uneven development of the internal glands or the attempt to harmonize their activities Marine ([3]) has shown that this condition is more prevalent in certain regions such as that of the Great Lakes The fact that this condition may be controlled by small doses of iodine offers a simple method of affecting this important period of development when it is complicated by thyroidism

Disturbance of the suprarenal glands has the opposite effect that of stimulating the gonad development and in the cases of precocious puberty a tumor of the suprarenals is often found In other cases there may be simply an overstimulation from the suprarenals which causes the noted precocity Each individual case of disturbed adolescence either delayed or precocious must receive careful study of the endocrine gland system to determine which glands are at fault Some very definite effects can be obtained from appropriate glandular treatment especially in cases where we can determine some definite derangement Many cases however, are most baffling and there is no field in medicine related to the adolescent period that needs more intelligent study than this of the endocrine system

Growth is not a simple nor a single process but is a multiplex phenomenon as described by Robertson ([4]) in his discussion of the growth factor found in the anterior lobe of the pituitary He states that "it would appear legitimate to infer that at a late stage in the third adolescent growth cycle the administration of excess of pituitary anterior lobe tissue leads to an acceleration of growth while at an earlier stage in the development of animals the administration of anterior lobe tissue leads to retardation of the rate of growth He concludes that "it is quite conceivable that pre adolescent hypopituitarism at a certain stage of development might yield effects in some respects analogous to those of late post adolescent hyperpituitarism He was able to produce such effects with the extract, tethelin which he obtained from the anterior

lobe completely changing the growth cycle of adolescence Clinically we see many cases which during adolescence undoubtedly show some disturbance in the normal development and secretion of the pituitary gland causing a disturbance in the normal progress of adolescence Besides the clear cut cases of hypo or hyper pituitarism we probably have many more cases in which there is a dys pituitarism connected with disturbances in some other gland most often in my experience this is connected with hypothyroidism

Treatment of Various Conditions

The treatment of these various conditions demands first of all a careful study of all the changes of the period of adolescence the anatomical physiological and psychological developments The anatomical and physiological disturbances are best handled by the most intelligent consideration of the details of life The amount of recreation needs careful regulation Sleep and rest are most important items Adolescence demands a more nutritive diet than any other period of life The school studies carried on in this country show that the food and the variety taken by adolescents far exceeds the demands of any other period amounting to from four to five thousand calories a day for boys The writer's own experience in studying the ravitaillement system in Belgium and the north of France emphasized the great ravages made in this period due to diminished food The period of adolescence stood out markedly as one which could not hold its own on the food ration of an adult This condition is now known to exist over all of war ravaged Europe and the adolescent period has suffered most from the stern restriction of diet caused by the war The varied psychological changes which have almost an infinite number of combinations and aspects need most sympathetic understanding and firm skilled handling As already indicated more than this the constant interrelation of all these changes must never be lost sight of as most often the study of the whole gives the key for the particular problem

Certain Problems of Adolescence

While all the varied changes of adolescence present many problems conduct which is the result of the individual effort to adjust himself to the demands of his environment during adolescence presents many of the most acute difficulties The mass of material accumulated by the juvenile courts of the country are crowded with instances of mal adjustment of bad conduct which results disastrously for the individual These cases represent in varying degrees the anatomical physiological and psycho

logical defects of adolescence Masturbation, which is one of the most frequent sexual acts indulged in by the adolescent boy and girl is found much more frequently in these cases of mal adjustment Where masturbation is a persistent factor, it is commonly associated with mental or moral defect

Healy ([2]) has carefully studied these problems of individual conduct and he urges the most intelligent study of the cases accompanied by an honest effort to adequately solve the problem Ordinarily this solution is left to the judge of the court In rare instances he has the advice of a trained psychologist In that case he may desire to act in the most intelligent manner but the judge has his limitations He can do one of three things place the delinquent child on probation, assign him to an institution, or drop the case If dropped without any attempt made to change the causes for the delinquency, the case will undoubtedly come up again Most institutions are overcrowded and not properly equipped for the *necessary training* either *in trained personnel* or the mechanics of handling the cases Probation officers are comparatively few in number and not particularly well trained Therefore the limitations of a judge of a juvenile court are not to be entirely laid at his door

The education of the community and the training of responsible public opinion to demand adequate laws and adequate budgets for carrying out the laws are absolutely necessary if these problems of conduct during the period of adolescence are to be adequately handled To gain this community responsibility psychopathic centers for the study of these adolescent problems are essential At such centers the best scientific medical and psychological studies can be carried out on these individual problems as they present themselves More than that such findings must be interpreted for and to the public in language understood and appreciated in order that the greatest factor in the whole problem of adolescent conduct may be met the factor of environment

Environment is after all a lay problem Only the very few in comparison to the need can have carefully planned and selected environment The average child passes his adolescence in the average community and that community must be educated in the needs and problems of adolescence The average community expression toward the adolescent child is either shown by constant repression or complete ignoring of the whole problem The records of the court prove this beyond any doubt Case after case of misconduct on the part of both girls and boys record the fact of stern denial on the part of parents to what might have remained *more or less normal activity on the child s part* or an absolute lack of interest in or knowledge of a child s activities which, allowed to seek

their own levels during the unstable periods of adolescence ended in broken laws

The physician s part is first of all the patient study of the period of adolescence and an appreciation of its effect on the conduct of the individual But his responsibility does not end here The education of the person controlling the environment of the individual case must also be undertaken by the physician if the results of his study are to be effective In this education of the parent the home and the community the physician must have the indispensable service of the medically trained psychological social worker It is interesting to note that the war has stimulated the formation of a course of training at Smith College for tho e social workers interested in the psychological and moral problems But the physician himself must emphasize and help interpret to the community the broader community responsibilities The kind of recreation offered to the adolescent child of any given community becomes the business of the physician because it is part of his treatment to recommend *proper recreation The dearth of opportunities for proper recreation* immediately appals the interested physician Cheap moving pictures dealing in so many instances with grotesque and vulgar suggestive humors or intense sex complications and the unsupervised dance halls make the problem most difficult for the doctor The adolescent child needs wholesome out of door exercise organized to permit of free self expression swimming properly supervised dancing dramatics Often the child of the poor is better off in these respects than the child of moderate circumstances or of the rich The settlement houses long ago recognized these problems and the club life of settlements has been the attempt to meet them

The Teaching of Social Hygiene

The war has forced the issue in sex education These words of Dr Mabel Ulrich in her telling pamphlet Mothers of America give the reason for this discussion here ( ) The past two years of public government propaganda has brought the subject of social hygiene out of the field of private endeavor to that of a distinct public health educational basis When the Surgeon General s Office (*) issues such facts as these namely that syphilis and gonorrhea have disabled more men in our army and navy than all other diseases combined that the draft has proved these diseases to be more frequent among the boys from our own home towns than among those in the regular army and that in spite of all that was done to prevent contagion at least 125 000 new cases developed among our drafted boys the field of social hygiene has become one

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normal whole The best time to differentiate sex distinction in a child s mind is before he becomes conscious of himself as of a sex When adolescence comes the avenue of approach to sex hygiene should be social rather than personal At no time in life is the need of a background of law more needed or more helpful than during the unstable years of adolescence One of the most clear and concise expressions of this is set forth in that splendid Children s Code prepared by William J Hutchins (7) The theme of the code is patriotism expressed in conduct The code is given in full because it states in the fewest words the constructive preventive program for the adolescent period

Boys and girls who are good Americans try to become strong and useful that our country may become ever greater and better Therefore they obey the laws of right living which the best Americans have always obeyed

The Good American Tries to Gain and to Keep Perfect Health — The welfare of our country depends upon those who try to be physically fit for their daily work Therefore 1 I will keep my clothes my body and my mind clean 2 I will avoid those habits which would harm me and will make and never break those habits which will help me 3 I will try to take such food sleep and exercise as will keep me in perfect health

The Good American Controls Himself —Those who best control themselves can best serve their country 1 I will control my Tongue and will not allow it to speak mean vulgar or profane words 2 I will control my Temper and will not get angry when people or things displease me 3 I will control my Thoughts and will not allow a foolish wish to spoil a wise purpose

The Good American is Reliable —Our country grows great and good as her citizens are able more fully to trust each other Therefore 1 I will be honest in word and in act I will not lie sneak or pretend nor will I keep the truth from those who have a right to it 2 I will not do wrong in the hope of not being found out I cannot hide the truth from myself and cannot often hide it from others 3 I will not take without permission what does not belong to me 4 I will do promptly what I have promised to do If I have made a foolish promise I will at once confess my mistake and I will try to make good any harm which my mistake may have caused I will so speak and act that people will find it easier to trust each other

The Good American Plays Fair —Clean play increases and trains one s strength and helps one to be more useful to one s country Therefore 1 I will not cheat nor will I play for keeps or for money If I

of the most burning of the public issues Here we are concerned with two aspects of the question the relation of preventive medicine to the field and its bearing upon adolescence, and the relation of adolescence to social hygiene The pre adolescent period is the time in which the foundation of the education in sex hygiene should be laid It is then that the questions as to the whys wheres and hows of life are asked and upon the frank meeting of these questions depends the future of adolescent attitude If before ten the child has met honest frank answers to his questions the later sex problems are the more readily approached with frankness and a minimum of sex consciousness

The importance of the pre adolescent question as to how life is created does not lie so much in the information given in the honest answer but in the frankness and beauty with which the question is discussed the maintenance of the unconscious curiosity of the child Sex consciousness as such seldom enters into the natural curious inquiry of the child under ten Sex then is merely accidental the why is asked about everything which brings new life, babies simply fall naturally into the category of interesting new life that is introduced into the child s immediate environment It is the same with a new kitten or calf The truth is wanted and should be given at the period but it bears no personal relation to the child while the way in which he is answered makes the more lasting impression The pre adolescent period has been left largely to the ignorance or lack of understanding of parents and the curiosity of other children which has brought to the adolescent period a false impress Preventive medicine must begin its work in the pre adolescent period if it is to have any comprehensive effect on the adolescent period

It is the business of the physician to stimulate the parents to equip themselves to meet these intimate problems of the children This can be done largely by intelligent direction on his part to the available literature on the subject and by giving to the parents his own comprehensive idea of the subject The child under ten grasps little of the detail of the information given him but the dramatic points the frank intimacy shared by him and his parents are his best preparation for the sex consciousness of the adolescent period The adolescent period marks the beginning of his consciousness that these questions that have stirred his curiosity and imagination are personal sex problems and that he must establish his relationship with them This sex consciousness results often in that impenetrable reserve often the attitude almost of fear that causes many of the complex psychoses of adolescence Information may be given at different times with varying degrees of detail to meet the particular problem facing the individual but the chief problem is to so relate the child to the whole life concept that sex becomes more and more a normal part of a

will be kind in all my Thoughts I will bear no spites or grudges I will not think myself above any other girl or boy just because I am of different race or color or condition I will never despise anybody 2 I will be kind in all my Speech I will not gossip nor will I speak unkindly of anyone Words may wound or heal 3 I will be kind in all my Acts I will not selfishly insist on having my own way I will always be polite Rude people are not good Americans I will not trouble unnecessarily those who do work for me I will do my best to prevent cruelty and will give my best help to those who need it most

The Good American is Loyal—If our America is to become ever greater and better her citizens must be loyal devotedly faithful in every relation of life 1 I will be loyal to my family In loyalty I will gladly obey my parents or those who are in their place I will do my best to help each member of my family to strength and usefulness 2 I will be loyal to my school In loyalty I will obey and help other pupils to obey those rules which further the good of all 3 I will be loyal to my town my state and my country In loyalty I will respect and help others to respect their laws and their courts of justice 4 I will be loyal to humanity In loyalty I will do my best to help the friendly relations of our country with every other country and to give to everyone in every land the best possible chance

If I try simply to be loyal to my family I may be disloyal to my school If I try simply to be loyal to my school I may be disloyal to my town my state and my country If I try simply to be loyal to my town state and country I may be disloyal to humanity I will try above all things else to be loyal to humanity then I shall surely be loyal to my country my state and my town to my school and to my family

Thus are given the social objectives by which the youth hitches his sex consciousness to the stars!

At the same time sex consciousness has its very definite physical aspects and developments and these must be explained and understood But all this is more possible when the child s relation to the larger physical and social life has been firmly developed in him Adolescence is not a pleasant period for a child—change and upheaval seldom are But the awakening of the sex life is for the great purpose of reproduction and even though the adolescent child may have no personal interest as yet in that great purpose he may be appealed to to play the game fairly in order that he may do his part when the time comes The period of adolescence always necessitates a restatement of the facts of life and then they are related to the new sex development physical rightness is the aspect to be most thoroughly emphasized because of its wider social responsibility

should not play fair the loser would lose the fun of the game and the winner would lose his self respect and the game itself would become a mean and often cruel business 2 I will treat my opponent with politeness 3 If I play in a group game I will play not for my own glory but for the success of my team and the fun of the game 4 I will be a good loser or a generous winner

' *The Good American Does His Duty*—The shirker or the willing idler lives upon the labor of others burdens others with the work which he ought to do himself He harms his fellow citizens and so harms his country 1 I will try to find out what my duty is WHAT I OUGHT TO DO and my duty I will do whether it is easy or hard What I ought to do I can do

The Good American Tries to Do the Right Thing in the Right Way—The welfare of our country depends upon those who have learned to do in the right way the things that ought to be done Therefore 1 I will get the best possible education and learn all that I can from those who have learned to do the right thing in the right way 2 I will take an interest in my work and will not be satisfied with slip shod and merely passable work A wheel or a rail or a nail carelessly made may cause the death of hundreds 3 I will try to do the right thing in the right way even when no one else sees or praises me But when I have done my best I will not envy those who have done better or have received larger reward Envy spoils the work and the worker

The Good American Works in Friendly Cooperation with His Fellow-workers—One man alone could not build a city or a great railroad One man alone would find it hard to build a house or a bridge That I may have bread men have sowed and reaped men have made plows and threshers men have built mills and mined coal men have made stoves and kept stores As we learn better how to work together the welfare of our country is advanced 1 In whatever work I do with others I will do my part and will help others do their part 2 I will keep in order the things which I use in my work When things are out of place they are often in the way and sometimes they are hard to find Disorder means confusion and the waste of time and patience 3 In all my work with others I will be cheerful Cheerlessness depresses all the workers and injures all the work 4 When I have received money for my work I will be neither a miser nor a spendthrift I will save or spend as one of the friendly workers of America

The Good American is Kind—In America those who are of different races colors and conditions must live together We are of many different sorts but we are one great people Every unkindness hurts the common life every kindness helps the common life Therefore 1 I

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CHAPTER XIV

AVIATION MEDICINE

By LOUIS HOPEWELL BAUER

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INTRODUCTION

Aviation is a comparatively new subject which had its origin in the rapid development of aeronautics which took place during the first World War. Except for the effects of high altitude, as observed in mountain expeditions and certain researches on the vestibular mechanism, nothing

Definitions — Aviation Medicine — Out of a mass of experience research and statistics a subject known now as aviation medicine has developed as a distinct specialty. This specialty is really a branch of preventive medicine as its sole basis is the prevention of aircraft accidents from the human standpoint. It has drawn to itself portions of other specialties namely physiology internal medicine ophthalmology otology neuropsychiatry and psychology. It is a correlation of certain parts of these specialties as they relate to flying. The specialist in aviation medicine is known as the flight surgeon.

The Flight Surgeon — The flight surgeon is a physician trained in aviation medicine. He is familiar with the branches of medicine concerned with aeronautics and their application thereto. He is skilled in making the various examinations required. He is sufficiently familiar with flying and its attendant strains and stresses to be a useful medical adviser to pilots and operators. He is familiar with the effects of oxygen want and lowered barometric pressure; he knows the effects of increased gravity drags on the human body and he knows how by applying his special knowledge he can prevent accidents from a physical standpoint by careful selection and careful supervision of flying personnel.

The flight surgeon is preferably a fairly young man as most flyers are young and they are more apt to make a confidant of one not too old. His personality must be one to inspire confidence and respect.

He should fly under all conditions and with all types of pilots. The flight surgeon who remains on the ground gets scant consideration from the flying personnel. He must experience the conditions the flyer meets almost daily in order to appreciate them and be competent to advise regarding their effect. He must have a thorough grounding in physiology of respiration and circulation in psychiatry and psychology in internal medicine and he must know sufficient ophthalmology to make the special examinations required and interpret their results.

Varieties of Flying

Flying is divided into heavier than air and lighter than air. Heavier than air flying is divided into military civilian and glider which may be either military or civilian and civilian flying into airline commercial and sport flying.

The requirements vary according to the type of flying to be done.

Military — Military flying is divided into fighting formerly known as pursuit air support and bombing. There are three types of bombers light medium and heavy.

was known pertaining to the physiology of flight Man was not designed by nature to fly and hence what its effect on him might be had hardly been considered

In the early days of flying at the time of the Wright brothers epochal accomplishment and for some time thereafter flying was hardly even a science A man was taught what he could be taught on the ground and then he tried to apply it in the air If he were lucky he flew If he were unlucky he was killed or severely injured The one physical attribute considered necessary was nerve and there is no doubt that it took plenty of that

Development in aeronautics was desultory until the first World War broke out and then the possibilities of flying from a military standpoint were so impressed on the Allies and the Central Powers that a tremendous advance was made from the mechanical standpoint The physical factor still was not considered especially important Only the ordinary physical examinations were required for duty in aviation services Soon however it became apparent that there were many accidents from a physical cause Pilots were wearing out too fast and there were too many deaths attributable to physical causes Research work stimulated by the necessity of man power conservation indicated that certain factors of a physical nature not important in ground fighting were paramount in the air

Gradually, therefore special examinations developed which became more or less similar in all countries By the time the United States entered the war much experience in the subject had been gained by the Allies of benefit to our own country As would be expected many mistakes were made stress was laid where it should not have been in some instances and other points which should have been stressed were overlooked

Following the war civil aeronautics began to develop in Europe although it was not until 1927 that any progress was made in this country It was found that civil flying is somewhat different in its demands from military flying and consequently the regulations had to be modified With the development of transport planes with their complicated instrument panels and safety devices with the increasing altitude of flight including flights into the stratosphere and with the steadily increasing speed of planes the medical aspects of flying became increasingly important Finally with the development of high altitude bombing and dive bombing the resulting onset of aero embolism and emphysema and the damaging effects of marked centrifugal force new problems have had to be conquered

The private pilot may fly for his own amusement or recreation but may not engage in any phase of commercial flying

The student of course is the novice learning to fly He must take his instruction from a licensed commercial pilot and in a licensed plane

The air line or commercial pilot does not in fact he is forbidden to indulge in acrobatics while flying commercially He flies over known territory adequately equipped with landing fields and beacons and the air line pilot in addition flies on a radio beam He may strike bad weather but an efficient meteorological service keeps him in touch with weather conditions His responsibility is heavy however as he has the lives of passengers in his hands Often his flying is done at night While commercial flying does not call for quite the same qualifications as certain phases of military flying nevertheless it does call for physical soundness and technical proficiency

The commercial pilot is a potential transport pilot and therefore the same applies to him

The private pilot may reasonably have a lower physical standard than the transport grade He however must meet a standard that insures his not being a menace to other flyers and the general public

Blind flying has become essential for air line pilots in order to insure safety in unexpected or expected poor weather conditions or above the clouds Transport flying is fatiguing and calls for endurance and sober judgment as well as constant alertness and keenness

Taken as a whole air line flying and military flying are equally difficult and call for the highest type of physical and mental makeup

Lighter than air — Lighter than air flying pertains to airships dirigibles and blimps and to balloons The general physical requirements need not be so high in that visual defects may be corrected with glasses Minor structural defects may be passed also

Glider Pilots — Glider pilots fly motorless planes Originally this was a sport only Now however it has become a military function also as often great fleets of gliders are used to transport troops The physical qualifications of glider pilots have not been definitely set but they should be at least those of private pilots

Physical Requirements of Flying

At the present time we may group the physical standards of aeronautics into two distinct classes First the standard for the military pilot and the commercial pilot and second the standard for the private or sport pilot

Pursuit — Acrobatic flying which we sometimes think of as stunt flying is absolutely essential for a military pilot For the combat pilot it is life saving The pursuit or fighter plane is fast and easily maneuverable It is a single seater The pilot s decisions must be automatic He must always be one jump ahead of his opponent His vision must be perfect He must be able to identify other aircraft in the air often by silhouette alone His depth perception must be perfect as he flies in formation with only a few feet between wing tips His reaction time must be immediate and his coolness in danger is absolutely essential The fighter pilot must not only be a flyer but a gunner

Air Support — This includes military flying not covered by the fighters and bombers It includes support of the ground troops with attack by machine guns and small bombs

Bombardment — This has become more complicated during the present war The heavy bombers are 4 motored ships and virtually flying fortresses with a crew of several men including pilot co pilot, navigator radioman gunners and bombardiers They fly at high altitudes and for long distances Then there are the medium bombers which are faster but have a shorter range and are small They are used for either horizontal or dive bombing In dive bombing the planes swoop down from a high altitude drop their bombs and zoom up again These pilots are subject to change of direction at speeds up to 500 miles an hour Light bombers fly at low altitudes and attack troops

Naval — Naval pilots besides the above have to learn to land on the deck of a carrier which calls for coolness and excellent depth perception Landing on the water calls for more accurate depth perception than landing on land

As a whole military flying is a young man s game fighter and dive bombing flying calling for the greatest skill quickest reaction time greatest daring and coolness Long and moderate distance high altitude bombing probably are a close second

Civil Flying — Civil flying in the United States is divided into three classes (1) air line (2) commercial and commercial lighter than air and (3) private student and private or student lighter than air and free balloon

The air line pilot flies commercial transport planes day and night over scheduled air routes He is responsible for passengers mail freight and property He must be an accomplished pilot navigator radioman and blind flyer

The commercial pilot either heavier or lighter than air carries passengers and often is an instructor He may be a co pilot on an air line

military and passenger carrying pilots should be examined by the perimeter on an eight point field

Central color vision is almost universally recognized as important for the flyer He needs to detect colored lights on the airdrome navigating lights on other ships colored signal panels and signal lights and what is

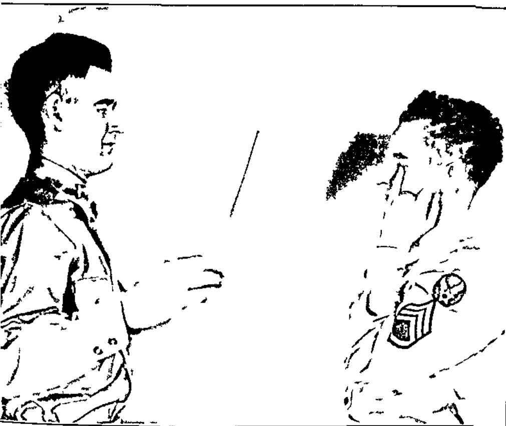


Fig 1 Confrontation test for gross peripheral visual field determination (Courtesy The School of Aviation Medicine Randolph Field Texas)

more important to determine from the color the character of the terrain over which he is flying in case of an emergency landing As one ascends the perspective of the third dimension gradually fades and one depends more and more on color vision to identify the characteristics of the terrain

The Ishihara and Stillings plates which are used by many countries are delicate color tests Many cases of partial color blindness are de

The detailed requirements may be obtained in the regulations of the various countries. They vary somewhat but more in methods of examination than in actual standards. In this chapter we shall discuss requirements in general rather than in detail.

The Eye

Central Vision.—It is recognized both by the physicians concerned and by successful pilots that good vision is a prime necessity. Not only is it of importance to the military pilot who has fighting, bombing or reconnaissance to carry out, but it is important to any flyer. Traffic in the air is rather congested at many airports and the obstructions around many airports are not always easily seen. Planes in the air must be detected. When two ships are traveling at a rate of well over 300 miles per hour they cannot be seen by each other too promptly. By good vision is meant normal vision without correction. Corrected vision, while permitted in the private pilot, is a poor substitute for good, uncorrected vision. Corrections worn in goggles are very unsatisfactory as they correct only straight ahead vision and when misted or fogged necessitating their removal the pilot is rendered helpless. Furthermore the wearing of corrected goggles restricts the peripheral field of vision. With the development of cabin planes there is less objection to moderate corrections being worn as glasses.

Practically all countries require for military and air line pilots normal or 20/20 vision in each eye uncorrected. Some countries, notably France, Holland and Hungary, permit one eye to be 25 per cent less than normal if the other eye be normal. Germany accepts 80 per cent of the normal in both eyes. For private pilots the standard varies but the majority require at least two thirds normal vision or better with correction.

During the present war standards of visual acuity in several countries have become gradually lowered owing to the shortage of man power with normal vision. Neither the United States Army nor Navy, however, has yet lowered its visual standards.

Peripheral Vision.—Peripheral vision is important for the flyer must see on all sides of him at once, particularly in landing, taking off, in formation flying and above all when on a military mission. Peripheral vision is also of importance in night flying, as defects of the color fields are sometimes associated with night blindness.

Visual fields are tested by means of a perimeter or campimeter in the great majority of countries. The notable exception is Great Britain, which relies on the confrontation test. Berens[6] believes that all

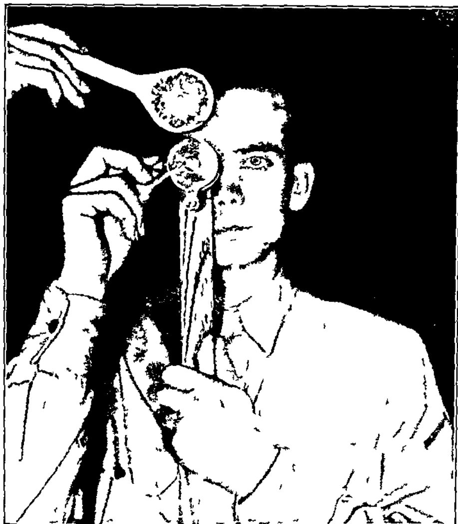


FIG 2 Determination of heterophoria (Courtesy The School of Aviation Medicine Randolph Field Texas)

commercial flying It is also tested in certain other countries but not with the same detail Berens[6] states that latent heterophoria often becomes manifest or results in diplopia under flying conditions It certainly is a fact that fatigue and high altitude affect ocular muscle balance Flying certainly is fatiguing Heterophoria is a suppressed condition It

tected by them that are not revealed by a simple test such as the Holmgren or Jennings It is questionable whether such perfect color vision is essential in flying The Department of Commerce does not require anything more than correct identification of individual colors

A study of partial red green color blind cases by Cooper[9] revealed that only 14 per cent of partially color blind students were able to obtain licenses as against 30 per cent of the normal Wright[36] states those of you who have flown along the air lanes at night in thick weather and tried to distinguish the red flashing intervals between the white beacon lights from those which flash green, know how difficult a matter it is at best The red backed beacons denote the course of the flight and the green backed beacons indicate emergency landing fields Any serious defect in color vision would certainly make it difficult for a pilot to distinguish the two in rainy or foggy weather The wind tees which indicate the direction of the wind at air fields often are lighted at night by green or red neon tubes which are not brilliant shades of the color they are supposed to represent and show shades which are difficult for color blind persons to distinguish from other nearby lights In the daytime, if a forced landing is to be made an instantaneous decision must be arrived at as to which field is to be used for the attempt at landing Inasmuch as the length of the grass the presence of holes or irregularities of the ground are only discernible from above by the different shades of green in a grass field and because the undertone of brown in a marsh may look similar to the overtone of green to a color blind pilot who is above this type of ground we believe that the element of danger is considerably increased by allowing color blind pilots to fly passengers

Light Perception — Light perception is now considered by more and more countries Berens[6] states that night flying and flying at dusk necessitates normal light perception Onfray[6] believes that the visual acuity at night should be equal at least to $\frac{1}{80}$ for an illumination of 0 0015 lux after 20 minutes of adaptation Flynn[1] recently has described a clinical test for dark adaptation which he feels every pilot should be required to pass It consumes but five minutes It is important also in bringing out avitaminosis Of 32 pilots who were demonstrated to have a deficiency in dark adaptation 22 were successfully treated with 10 000 units of vitamin A three times a day for fourteen days Three weeks after the treatment all were retested and found to be well within normal limits In 500 cases tested 6 4 per cent were found to be deficient in vitamin A

Ocular Muscle Balance — Ocular muscle balance is tested in the United States rather more carefully in the military services than in

Accommodation — Accommodation is not universally tested but the United States requires a certain amount of accommodation. The Army and the Department of Commerce require a minimum of 2 diopters. The Navy requires normal accommodation for age. The flyer must rapidly

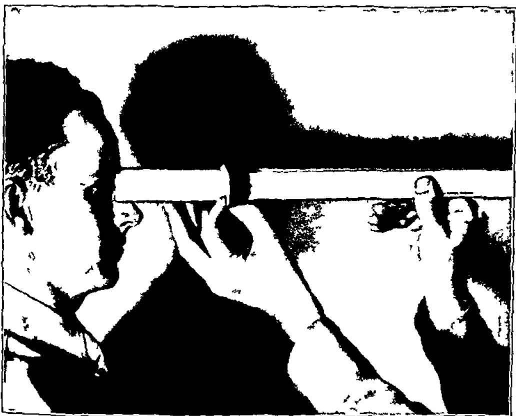


Fig 4. Determination of the near point of accommodation. (Courtesy The School of Aviation Medicine, Randolph Field, Texas.)

change his accommodation from that required for reading his maps and instrument board to the relaxation necessary for observing distant objects.

Depth Perception — Judgment of distance is a highly important factor. The flyer must judge distance when taking off or landing from the ground, trees, buildings, telephone poles, wires, other planes, etc. In formation flying the wing tips are but a few feet apart and a miscalculation of distance may prove fatal.

causes fatigue and results in inattention and eventually carelessness Poor muscle balance is also a factor in faulty judgment of distance as will be seen later

Limits of 1 diopter of hyperphoria and a minimum of 7 diopters of convergence and 3 diopters of divergence are accepted for civilian flyers in this country also there must be no diplopia develop with the head in



Fig 3 Red lens test for determination of diplopia (Courtesy The School of Aviation Medicine Randolph Field Texas)

any position except extreme angles on gazing at a light 20 feet distant with a red glass in front of one eye The military services also test esophoria and exophoria at 20 feet and 33 inches and the angle of convergence also is measured The British use the red green test and the Bishop Harman apparatus Berens[6] believes the near point of convergence is important and that any near point over 80 mm should be disqualifying

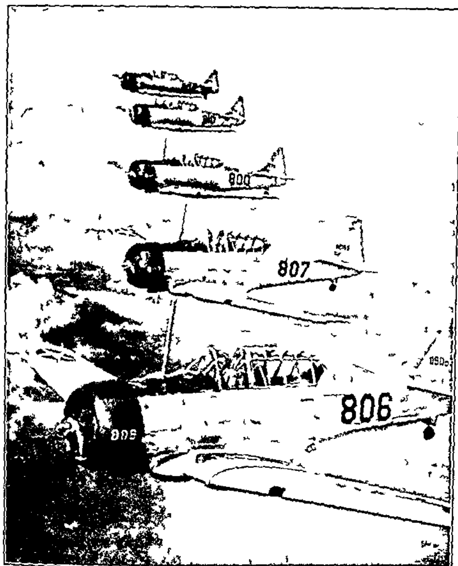


Fig 6 Formation flying This calls for excellent depth perception (Courtesy Photo Section U S Army Air Force)

No special tests of depth perception or judgment of distance are required by many countries as they depend entirely on visual acuity and normal muscle balance Some countries require a test of stereoscopic



FIG 5 The Howard depth perception apparatus in operation The candidate is seated 20 feet away from the apparatus and looks at the rods through the window in the front The rods are widely separated and he endeavors to bring them parallel At least three trials are given and the average discrepancy must not be more than 30 mm The apparatus is 40 long and 1[illegible] wide The front and rear ends are 1[illegible] square The window in the front end is 5 by 7½ The rods are 10¾ high and [illegible] in diameter One rod is fixed and the other moves forward or backward in a slide groove The entire apparatus is painted black except the front face of the rear screen which is painted white (Courtesy The School of Aviation Medicine Randolph Field Texas)

Hearing — So far as hearing is concerned up until recently it was not considered very important It is well known that the majority of old flyers old in the sense of experience have diminished hearing This is due to the constant roar of the motor or motors Protection is advised but flyers for some reason are loath to wear it The majority of pilots flying open ships wear large sized powder puffs sewn into the ear flaps of the helmets but pilots of closed ships rarely wear any protection In closed ships the noise is not nearly so severe but even there it is sufficient to damage hearing

Furthermore the increased use of radio has made the use of any protection difficult The pilot likes to keep his radio tuned in as low as possible Wright[16] reported that a radio head piece with cup shaped ear phones with sponge rubber inner surfaces was being worked out and it is hoped that it or some other device will prove satisfactory

The increased use of radio necessitates a certain amount of hearing and it is causing many of the older pilots some worry because they feel they are losing their hearing It is a fact however that the pilots who are somewhat deaf to ordinary tones can still hear radio signals the tones required by the radio not being those to which they are deaf Good hearing then should be required in all pilots who are starting in with the idea of becoming commercial or military pilots McFarland and associates[5] reported that with increasing age there was a gradual decrease in acuity of hearing the higher frequencies He found this decrease was the same in non flyers

Equilibrium

This has been a much discussed point During World War I two thirds of the articles written by Americans were on the vestibular mechanism of the internal ear The Barany tests were stressed and made much of The French and Italians used them largely also The British never did have any use for them The Barany tests are now largely in the discard so far as flying is concerned In this country they are used only by the Navy The Army formerly used the British self balancing test but has since discarded it The Army now has no specific test of equilibrium as such The Barany chair may be used as an emotional stimulus in cases of suspected neurocirculatory asthenia and doubtful nervous stability

The Department of Commerce uses the self balancing test alone It consists in demonstrating the ability to stand on one foot with the other leg flexed at the knee with the eyes closed for 15 seconds Three trials

vision with a stereoscope The United States uses the Howard depth perception apparatus[16] requiring a depth perception of not more than 30 mm at 20 feet on the average of several trials

Stereoscopic vision requires two eyes and hence monocular individuals and those who have markedly different vision in the two eyes usually have poor depth perception Poor ocular muscle balance also affects depth perception adversely Clements of the Royal Air Force found that many students making poor landings were doing this because of defective ocular muscle balance and on having this defect corrected 87 per cent of them made satisfactory landings

There are a few one eyed pilots who can judge distance fairly well and are good flyers There is no question but these men acquire a method of judging distance which the average two eyed man does not use Jarman[1] believes this to be by means of moving the head from side to side Having lost the function of binocular parallax he uses one eye twice in an endeavor to make up for this loss of normal function Only old experienced pilots however should be considered for waiver of such a serious defect

The time factor usually is not considered in this test but it undoubtedly is an important factor as the individual who judges distance quickly as well as accurately is safer than one who judges it slowly although perhaps as accurately

Ocular Disease — The eyes are inspected and the fundi examined for ocular disease and abnormalities and diseased conditions which revealed serve as a cause for rejection

The Ear Nose and Throat

The ear nose and throat are surveyed for defects and disease It has been demonstrated that under exposure to cold and extremes of weather and as a result of fatigue in flying diseased tonsils sinuses and low grade ear infections are apt to light up into acute infections Such should therefore be eliminated at the start

Requirements are much more rigid in the military services than in civilian flying The military services require a practically perfect ear nose and throat for selection The commercial flyers are not rejected for minor abnormalities and in the private pilot gross defects sometimes are passed such as perforated ear drums for example Middle ear conditions usually are accompanied by blocked or partially blocked Eustachian tubes and on sudden changes of altitude the ear drum may be ruptured or at least its sudden retraction may cause excruciating pain

are given It is then repeated on the other foot It is satisfactory for all practical purposes and does away with cumbersome apparatus that at best was not wholly satisfactory

Equilibrium depends on the sensations received from our whole proprioceptive mechanism Its various parts cannot be considered too individually Vision is undoubtedly the most important factor in the flyer The tactile sense is largely non functioning in a flyer but the internal ear visceral sensations and sensations received from the bones joints and muscles should be considered collectively

Equilibrium has received a new importance with the advent of blind flying, of which more will be said later

The General Physical Requirements

The general physical requirements are the requirements of any thorough physical selection Sound heart lungs kidneys a normal endocrine system freedom from structural defects and disturbances of cardiovascular function and a good medical history are required and are essential The examination consists of a thorough physical examination

Stature —Stature is not so important as it used to be but a very small or a very large man is not ideal because of the resultant mechanical difficulty in reaching or operating the controls Men of average stature are preferred for fighter pilots rather than very tall men

Age —Age is a disputed factor but flying is still for the younger generation After 35 to 40 a conservatism and slowness of reaction develop that prevent one from becoming a high class flyer if he does not learn until that age Those who learned young and are now between 40 and 50 years of age are in a different class They have passed the most difficult stage of their careers namely *training and early experience* They seem to continue to do well *Fighter and dive bomber pilots definitely are preferred of the younger age below 28 years* The international regulations impose an age limit of 19 to 45 for transport license

Structural Factors —Complete use of the four limbs is an international requirement Loss of 2 or 3 fingers slight limitations of motion of the ankle wrist or knee may be permitted but complete mobility of shoulder elbow and hip are essential and only minor limitations of the excepted joints permitted The manipulation of the controls brakes and stabilizer require this much as a safety factor There are a few pilots flying who have had one leg amputated below the knee but they all learned to fly before the amputation and are in a special class therefore *Hernias in the case of transport or military pilots should disqualify until they are*



FIG 7 The self balancing test for equilibrium (Courtesy The School of Aviation Medicine Randolph Field Texas)

Syphilis — Syphilis is of course disqualifying. A Wassermann reaction is not required for a commercial license unless a history or suspicious signs are unearthed. It would be best if a Wassermann test was required on all prospective commercial pilots. The military do require it of course as a prerequisite to commission.

The Nervous System

The nervous system was passed over superficially in the early days of flying. Other than examination by means of a few neurological tests such as pupillary reactions, station, knee jerks, etc., nothing was done.

It soon became apparent that the nervous system was subject to great wear and tear in flying, and one of the commonest causes for removal from flying status was nervous instability. Consequently the development of a searching neuropsychic examination took place. It has reached its highest peak in this country in the Army examination. The Navy and Department of Commerce also require searching examinations.

For practical purposes the following points are all that it is necessary to cover.

Neurological Examination. — (1) Pupillary abnormalities, the cause of which must if possible be elicited and syphilitic conditions suspected.

(2) Knee jerks, with the usual interpretation of findings.

(3) Station: both a Romberg and modified Romberg are done, which must be satisfactory.

(4) Gait: walking backward, forward and in a circle with eyes open and closed.

(5) Tics, the presence of which leads one to suspect an unstable nervous system.

(6) Tremors of hands, eyelids and tongue: if abnormal, neurological conditions, hyperthyroidism and neurocirculatory asthenia must be considered.

(7) Other motor abnormalities such as residual from infantile paralysis.

(8) Psychomotor tension: the ability to relax voluntarily. If unable to relax, the applicant usually is emotionally unstable and will not learn to fly readily.

(9) Peripheral circulatory flushing, mottling, acrocyanosis, sweating, cold extremities, the presence of which suggest neurocirculatory asthenia or a more serious nervous system derangement.

Psychic Examination. — This part of the examination, as Longacre[19] so aptly states, "should begin when the candidate first comes into view and ends only when he has passed from sight and hearing."

required Flying often is strenuous and strangulation a danger

General — The military of course require freedom from organic disease of the heart lungs kidneys endocrine glands and digestive system That pilots who are to carry passengers should likewise be physically sound goes without saying There are a few exceptions An old arrested tuberculosis without symptoms may be passed for commercial flying Acute infections need be causes for rejection only temporarily unless they leave manifestly disqualifying defects

Cardiovascular System — The cardiovascular system should not only be free from organic disease but there should be no evidence of neurocirculatory asthenia The nervous mechanism is under a severe strain in flying anyway and the weak sister drops by the wayside More will be said of this under the nervous system

Fatigue altitude and stress all impose strain on the cardiovascular mechanism and hence it must be normal to start with Many applicants come in for their first examination in a state of apprehension High pulses and blood pressures are encountered frequently The examiner must eliminate organic cardiovascular disease thyroid disease and neurocirculatory asthenia Reassurance and obtaining the confidence of the applicant often will result in the pulse and blood pressure returning to reasonable limits The response of the pulse to exercise and the length of time it takes it to return to its pre exercise rate are often more important than the rate itself Any pulse that gives an exaggerated response to exercise and is slow in returning should be a cause for rejection even if no organic disease is demonstrable Such an applicant probably is in the class of the nervously unstable and will make poor flying material Those applicants who show hypertension on several examinations but who have no history of hypertension when not under stress rarely make good pilots Many are potential cases of essential hypertension and most of them are somewhat emotionally unstable

Urine Examination — Nephrosis nephritis and diabetes are of course disqualifying because of the serious constitutional effects A urine examination is manifestly a requirement

Digestive System — The digestive system seems to be particularly important in flyers They have irregular hours and irregular meals with food of all kinds and at all sorts of places their bowels may of necessity be irregular because of their flying schedules and disturbances of the gastrointestinal tract are common Hence the history of any symptoms suggesting ulcer gall bladder disturbance colitis etc must be gone into with considerable care and all cases that seem to have a definite gastro-intestinal condition should be rejected

ically unable to analyze and correct errors inconsistent erratic from day to day poor on simple manœuvres and lost in acrobatics unable to absorb or retain instructions poor in speed distance coordination altitudes and balance no feel of ship does not realize his mistakes or when he is right and when he is wrong unable to sense slips skids stalls etc easily confused lacks initiative and aggressiveness learns nothing for himself fusses with controls inattentive to instruments traffic obstacles wind directions jerky and rough on controls kicks or rides the rudder mechanical flyer and in connection with that one instructor very aptly completes the picture by saying no instinctive performance all mechanical unable to coordinate controls headwork poor judgment poor tense apprehensive nervous and excitable danger in power off poor headwork on forced landing excitable and blows up on slightest provocation had difficulty because left handed repeats his mistakes over and over again forgets instruction over night over the week end over the Christmas holidays and so on perhaps too much diversified interest inattentive to details reaches his saturation point and fails to progress concentrates on flying the plane to the exclusion of everything else i e he excludes every factor in the environment he is oblivious to the traffic the wind directions lights and everything of that sort lets plane fly never seems to control it hopelessly unable to fly entirely out of his element too easily confused unable to execute manœuvres requiring finer timing and coordination unable to decide promptly and act decisively unable to relax He states that of 687 failures 404 were reported as incurably tense and apprehensive

Carlson[8] reported that instructors washed out students frequently with the following remarks slow learner poor comprehension poor retention poor headwork slow progress unable to understand forgets instructions

Longacre[19] further states the following traits are indices of such future poor performance and in a careful examination could be unearthed in decisiveness inattentiveness uncertainty indefiniteness evasiveness hesitancy timidity overdeveloped self preservative instinct vagueness superficiality recklessness clumsiness awkwardness slow comprehension delayed or slow motor response sluggishness poor retention lack of initiative and aggressiveness self depreciation tenseness inability to relax being oversensitive being unduly introspective being handicapped by an inability to respond correctly to diversified stimuli i e to instruments ships etc and environments simultaneously

We must therefore endeavor to forecast the candidate s probable reaction to this new experience of flying Again to quote Longacre[19]

Loc. cit. 343

The psychic examination specifically includes a search for a family history of epilepsy hyperthyroidism psychosis and psychoneurosis The family history of any may indicate a transmitted nervous instability Past personal history should be searching and covers not only the history of severe illnesses and injuries but a complete personality study is made This covers childhood environment and reaction to discipline educational history and progress athletic life social trends somatic demands self expression psychomotor activity self criticism temperament philosophy of life

Longacre[19] has stated that the purpose of this personality study is to study the condition of the candidate s nervous system An effort is made to determine whether or not there are deviations from the normal and if so whether or not these deviations are sufficient to disqualify him from flying to study the candidate s temperament intelligence and volition and again to determine deviations from normal for the same reason to study the manner of the candidate s reaction to his environment and to unearth latent tendencies which under the stress of flying might become accentuated in such a manner as to render him inefficient and to determine the personality trends resistances and potentialities

During this personality study we may find the following favorable factors (a) Temperament — Cheerful stable self reliant aggressive modest frank fond of people satisfied punctilious serious good cooperation in work and in examination good sportsmanship moderate tension enthusiastic adaptable (b) Intelligence — Precise penetrating sharp alert resourceful (c) Volition — Energetic quick deliberate or moderately impulsive controlled, good tenacity of purpose

We may also find the following unfavorable factors (a) Temperament — Depressed unstable submissive pacific vain withholding secretive loquacious likes to be alone hypercritical of conditions careless frivolous poor cooperation irritable poor sportsmanship (under adverse circumstances querulous and complaining) exceedingly high tension lost enthusiasm (b) Intelligence — Vague superficial dull hesitant without initiative untrained (c) Volition — Sluggish slow recklessly impulsive restless poor tenacity of purpose

No one of course will exhibit all favorable or all unfavorable factors but the preponderance one way or the other will determine whether or not he will make a satisfactory flyer The importance of this part of the examination will be realized when a study is made of the reasons given by instructors why men fail to learn to fly Longacre[20] made such a study of the failures at the Army primary flying school He found the following reasons for failure as stated by the instructors slow mentally and phys-

ing in it were purely a matter of personal opinion of the operator There was no graphic record and it has been discarded

The Reid reaction apparatus is an improvement in that it has a graphic record of the candidate s performance It consists of the cockpit of a plane fitted with seat stick and rudder bar On the instrument

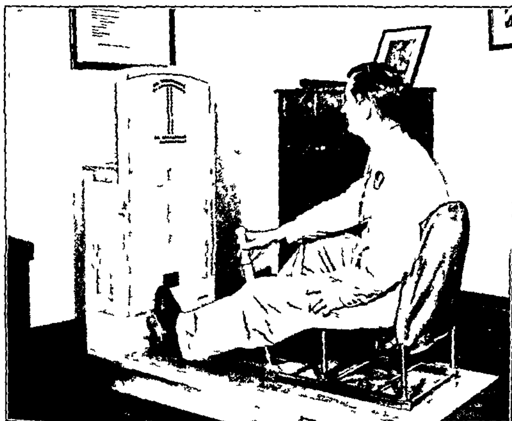


FIG 8 The serial reaction apparatus in operation (Courtesy The School of Aviation Medicine Randolph Field Texas)

board are two rows of lights one for the stick and one for the rudder When in an extreme position all the lights are lighted They gradually go out as the controls approach neutral Whenever the controls are off neutral a recording pen continues writing until the neutral point is reached and maintained A chronometer measures the length of time in fractions of a second that the controls are off neutral

the examination must reveal latent tendencies which under the stress of flying might become so accentuated as to make him the pilot inefficient and lead to nervous and mental breakdown or on the other hand make clear such stability of organization as will be proof against stresses admittedly exceptional and foreign to average experience It is not conceded that nature has at last achieved her highest objective and in the flyer produced a superman It is however required that he be equal to the requirements of any situation usual or unusual and with respect to the unusual be capable of the instantaneous and correct response demanded by the emergency

Vasomotor Instability — Examination for this condition is conducted as part of the cardiovascular examination and as part of the neuropsychic examination The Army[11] states that if persistently present in marked degree it is disqualifying for pilot training The following manifestations are listed (1) rapid pulse (2) labile pulse (3) labile low blood pressure (4) low Schneider index (5) cyanotic extremities (6) cold clammy extremities (7) mottling of extremities (8) profuse axillary perspiration (9) palmar and plantar perspiration (10) tremors of extended hands (11) tremors of closed eyelids (12) tremulousness of muscles of face and lips (13) tremulousness of speech

In each case the flight surgeon is cautioned to evaluate any of the signs of vasomotor instability with all the other findings in the complete examination to determine the individual s ability to withstand the signs of military aviation

Reaction Time and Flying Aptitude

Reaction time has always been considered an important factor in flying and various attempts have been made to devise a satisfactory apparatus During World War I simple reaction times were tested but they have been discarded nearly universally as being worthless It was found that the promptness with which an individual might tap a telegraph key in response to a stimulus of a light a bell or an electrode on the hand was no indication of how he might respond with a complicated arm and leg movement under the proper stimulus in the air

The Ruggles orientator was devised in this country and was used considerably It consisted of the cockpit of an airplane suspended in three concentric rings controlled by motors and governed either from the cockpit or the ground The candidate could be placed in every conceivable position with relation to the horizon and put through any rotary motion The disadvantage of the apparatus was that the results of train

ing in it were purely a matter of personal opinion of the operator There was no graphic record and it has been discarded

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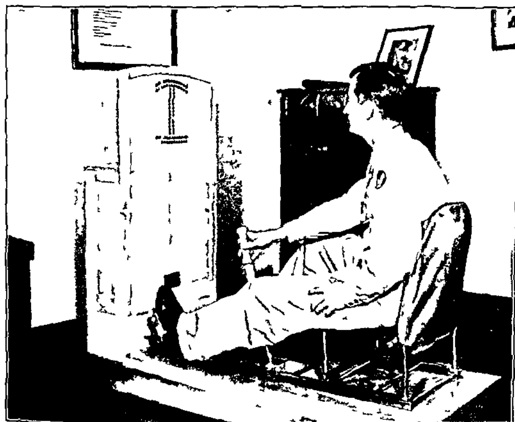


Fig 8 The serial reaction apparatus in operation (Courtesy The School of Aviation Medicine Randolph Field Texas)

board are two rows of lights one for the stick and one for the rudder When in an extreme position all the lights are lighted They gradually go out as the controls approach neutral Whenever the controls are off neutral a recording pen continues writing until the neutral point is reached and maintained A chronometer measures the length of time in fractions of a second that the controls are off neutral

The test after a practice period consists in having the controls placed in an extreme position The chronograph starts the pen writes and the length of time it takes to neutralize the controls is recorded graphically Ten tests of rudder 10 of stick and 20 of combined stick and rudder are so made Then while one test is being made a klaxon horn back of the candidate is blown suddenly and the effect of the emotional disturbance in prolonging reaction time is noted and also in succeeding tests the length of time it takes to come back to his average performance before the horn was blown

The average reaction time is figured and the candidate rated accordingly The British claim remarkable results with it They state that there is an 80 to 90 per cent correlation between the results of the test and the actual flying record in the schools of instruction

The slower the reaction time the poorer the flyer as a rule and any one whose reaction time is below 4 seconds is not considered worth training and those who cannot do better than 3 5 seconds probably will make only mediocre pilots at best

A serial reaction apparatus was devised in 1934 by Mashburn and Constable and reported by Mashburn as an automatic apparatus designed to present a continuous series of stimuli[1] The responses to the signals are made by a coordinated movement of a series of controls operated by the hands and feet The correct response to a set of signals automatically sets up the succeeding signals until the whole series is completed A reactor s score is the total time required to run through the complete series

This test still is being used at certain reception centers in the Army in conjunction with five other psychomotor tests in an effort to find a group of tests which will have a high correlation rate with the successful completion of flying training

For commercial flying no such complicated tests and no expensive apparatus as those just described can be used We must depend on the neuropsychic examination already outlined With careful examinations and with particular lookout for the factors enumerated by Longacre as indicating poor aptitude we can arrive at fairly satisfactory results

The Army has adopted an adaptability rating for military aeronautics aptitude[35] This is based on an even more detailed personality study than the one outlined under the nervous system The following factors are studied and a maximum rate for each factor is reckoned as follows on the next page

Family history	05
Environment	05
Morphology	10
Intelligence	60
Achievement	20
Psychomotor activity	20
Emotionality	35
Somatic demands	25
Sociality	15
Philosophy of life	05
Total	200

160 points are required to qualify An unsatisfactory adaptability rating must be supported by at least one of the following 18 reasons (1) history of multiple 2 or more instances of mental disturbances in the immediate family (father mother and siblings) (2) intelligence is considered below the required standard because of (a) many failures in the grades and high school requiring extra months or years to complete high school (b) inability to accomplish two years of college work because of many academic failures (c) complete lack of accomplishment to date and failure to take advantage of opportunities (school and work) (d) specific instances of applicant s behavior indicating questionable intelligence Record must be made of evidence demonstrating poor judgment poor comprehension poor memory poor attention poor learning or other faulty intellectual operations These must be so obvious that they outweigh any educational attainments (3) a history of somnambulism (4) a history of stammering or presence of a tic (5) a history of migraine or migraine type of headache (6) a history of amnesia (psychogenic) (7) a history of skull fracture or severe concussion with persistent symptoms any period of unconsciousness of 2 hours or longer (8) a history of epilepsy or convulsions (9) a history of fainting due to inadequate cause subsequent to age 12 the only adequate causes being (a) pain following a severe injury (b) during convalescence from an acute illness (c) moderate to severe loss of blood (10) persistent insomnia (anxiety) (11) obsessions or phobias which motivate conduct (12) instability manifest by combinations of the following one or even two not necessarily disqualifying (a) convulsions in minor illness (b) prolonged enuresis if to present time it alone is disqualifying (c) frequent headaches (d) multiple histories of momentary unconsciousness in minor injuries (e) pavor nocturnus (anxiety) (f) mild insomnia (anxiety) (g) nail biting (h) mannerisms (i) excessive tobacco (j) a

low Schneider index (k) tenseness (13) excessive alcohol or criminal history (14) any major psychosis (15) any minor psychosis (psycho neurosis) (16) any constitutional psychopathic state (17) the following personality trends if present to a considerable degree seclusive overactive depressive suspicious egotistical irritable sexually abnormal and criminalistic (18) any neurological disqualification

Periodicity of Examinations

All countries require some sort of physical examinations for their military air forces and most countries require stringent examinations as already described for both military and civilian pilots The United States and many other countries require a satisfactory physical examination for flying before an individual may solo in licensed aircraft It is a universal practice to require re examinations of licensed pilots at stated interval All civil pilots are examined once a year Air line pilots are examined at least twice a year All pilots must be re examined following an accident before resuming flying The United States requires its military pilots to be re examined twice a year The mid year examination is only a check of the more important points The annual examination is complete Following accidents or serious illness an examination is required also before resuming flying Air line pilots in the United States are examined at least twice annually and other pilots annually

Physical Defect and Flying Ability

Much has been said already about the necessity of a normal physical makeup for flying and how the examinations for selection of the flyer have grown more stringent It may be well at this point to consider what happens to the flyer who is not physically sound particularly in his training period

Bauer and Cooper[9] studied the records of 9 000 students without previous experience and the records of about 2 000 accidents in trained flyers Later Cooper[10] carried it further to cover about 30 000 students and over 4 000 accidents

In the first study the records of all student pilots licensed by the U S Department of Commerce who had had a year or more since the issuance of their student permits in which to obtain a higher grade of license were studied No student was included who had had previous experience in flying The students were classified according to their physical condition The study showed that of those with no defects 35 4 per cent

obtained a private license or better in a year those with minor defects 30 3 per cent advanced those with major defects 18 5 per cent advanced and of those with disqualifying defects only 12 5 per cent advanced In other words as the defect increased in magnitude the less chance the individual had of learning to fly

Cooper s[10] study of 30 000 students showed similar but more marked discrepancies between the groups In this study the normal group showed a progress rate of 30 5 per cent the minor defect group 17 per cent the major defect group 14 7 per cent and the disqualified group 4 1 per cent He found also as to the group with disqualifying defects that all told 286 permits had been issued to students with disqualifying defects and of these 286 only 6 at the time of the study held a license of any sort In other words if regulations did not stop their flying nature did

Cooper[10] went a step further in this latter study and broke down the large groups into classes of defects As would be expected he found that some defects were more serious than others For example in the group of so called minor defects he found that mild structural defects and minor defects of hearing showed a progress rate of 21 5 per cent as against 17 per cent for the group as a whole and 30 5 per cent for the normals Moderate defects of color vision showed a progress rate of only 14 per cent thus bearing out Wright s contention already mentioned Those with high pulses and blood pressures had a progress rate of only 8 per cent This is in line with Longacre s findings that nervousness and apprehension are common causes of failure in learning to fly In the group of major defects defective vision showed a progress rate of 21 5 per cent as against 14 7 per cent for the group as a whole and 30 5 per cent for the normals general physical defects a rate of 5 8 per cent ocular muscle imbalance a rate of 4 1 per cent inferior neuropsychic makeup a rate of 3 5 per cent again emphasizing the importance of a sound nervous system while structural defects and defective equilibrium showed a rate of 0

All this proves rather conclusively that physical condition and the ability to learn to fly are closely related The greater the physical defect the poorer the chance of becoming a flyer

The study of accidents by Bauer and Cooper[9] showed that in 1928 the accident rate in normal pilots was 13 6 per cent in pilots with some physical defect the rate was 18 2 per cent In 1929 the rate for the normal group was 12 3 per cent and for the defective group 18 2 per cent Figured in another way in 1928 the percentage of normal pilots who had accidents was 10 5 per cent and the percentage of defective pilots who

had accidents was 18 5 per cent In 1929 the figures were 10 6 for the normal and 15 6 for the defective The normal pilots showed a fatality rate in accidents of 1 55 per cent and the defectives a rate of 2 36 per cent

Cooper[10] studied 4 227 accidents and considered the transport the limited commercial and the private pilots separately He found the private pilots who had physical defects had accidents $33\frac{1}{3}$ per cent more often than the normal and the fatal accidents were $66\frac{2}{3}$ per cent more numerous among the defective than among the normal In the limited commercial grade the figures were the same as for the private pilots for accidents and the fatal accidents were 50 per cent greater among the defectives than among the normal

In the transport grade the accident rate in the physically defective group was 50 per cent greater and the fatal accidents were the same in both groups Cooper explains the latter fact by stating that transport pilots in view of their greater experience are more apt to get out of serious situations with less damage

The work by Bauer and Cooper has been criticized as not being borne out by facts However Herbolsheimer[15] has just made a study of 300 unselected aviation accidents and found that the accident rate in pilots with physical impairments was one third greater than the ratio of physically defective pilots certificated This study was on reported civil air accidents in 1941

As a check the last 100 accidents reported up to August 1942 were analyzed and the figures were in close agreement with the 1941 figures From the results of the study Herbolsheimer states ' It appears safe to conclude that pilots with physical impairments can reasonably be expected to be involved in aviation accidents more frequently than persons with no impairments

These figures are not radically different from those of Cooper who found the rate of accidents in various types of pilots was from 33 to 50 per cent greater in the group with physical impairments

It has been alleged that flying experience is a greater deterrent of accidents than physical condition No one denies that the experienced pilot is less prone to accidents but it must be remembered that aviation accidents are apt to be fatal and hence as Herbolsheimer states there are few 'repeaters so that those prone to accidents are eliminated Furthermore in any study of experienced pilots the type of flying done type of aircraft flown whether local hops or cross country blind flying weather conditions etc must be known as they all affect the pilot s accident exposure

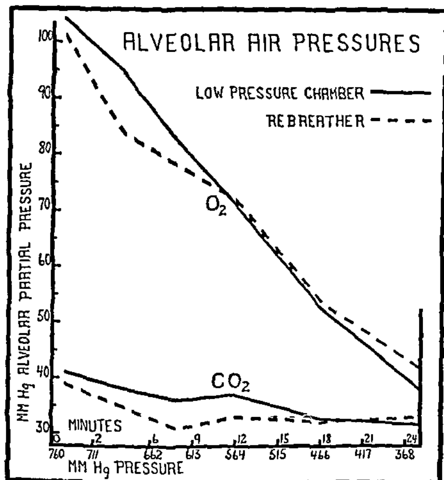


FIG 9 Alveolar air pressures (From Bauer Aviation Medicine courtesy Williams and Wilkins Co)

THE EFFECTS OF HIGH ALTITUDE

Military flying is being done at increasingly high altitudes 30 000 to 40 000 feet In commercial flying except when flying over mountainous country 8 000 feet is about the limit except in the so called stratosphere planes In crossing the Rocky Mountains altitudes of 10 000 to 14 000 feet may be reached Stratosphere planes are now in use on some of the

air lines They are really substratosphere planes and not stratosphere They fly at about 20 000 feet They have a hermetically sealed cabin in which the atmosphere is kept at a level which does not require supplementary oxygen Recently much has been heard about building planes that can fly in the stratosphere above 50 000 feet in order to take ad vantage of the wind direction and speed at that height

In this connection it must be borne in mind that the average unacclimatized person becomes unconscious without oxygen at about 25 000 feet With oxygen he may go considerably higher What the exact limit is varies probably with the individual his physical condition and weather conditions However it is somewhere near 47 000 feet At this level or near it the pressure of oxygen even when the individual is breathing pure oxygen from a supplementary supply is too low to sustain life and *the individual dies*

The early effects of oxygen want are evidenced by an increased volume of respiration per minute The pulse accelerates possibly in an effort at compensation but probably chiefly as a sign of distress The blood pressure may remain level until just before unconsciousness when there may be a gradual rise of the systolic pressure and a gradual fall of the diastolic In some cases either the systolic or diastolic pressure may fall suddenly causing circulatory failure with fainting

The effects of oxygen want on the brain are evidenced first by a feeling of exhilaration Then there is a loss of attention particularly a restriction of the field of attention and an inability to coordinate the finer muscular movements This may be seen experimentally in the handwriting of an individual Finally judgment is lost Vision and hearing do not diminish until just before unconsciousness The effects develop insidiously and frequently they are compared to the effects of alcohol Unconsciousness may ensue without the individual being at all aware of anything wrong

As one ascends into higher altitudes the barometric pressure gradu *ally falls and the oxygen* percentage remains *constant* The oxygen pressure in the atmosphere is determined by the formula

Oxygen percentage × barometric pressure

For example at sea level the oxygen pressure is 760 mm × 0 21 = 159+ mm Hg

Alveolar oxygen pressure determines the amount of oxygen absorbed into the blood Alveolar oxygen pressure is determined by deducting the pressure of water vapor accumulated in inspired air (47 mm at any level) and multiplying the remainder by the oxygen percentage The

oxygen percentage in the alveoli however is not 0 21 but approximately 0 145 per cent as it has become diluted by the time it reaches the alveoli Hence at sea level the alveolar oxygen pressure is

$$760 - 47 = 713 \times 145 = 103 + \text{mm}$$

As one ascends the alveolar oxygen pressure falls If one adds supplementary oxygen to the inspired air he increases the oxygen percentage and can therefore increase the alveolar oxygen pressure This as will be seen is true only up to a certain point

The pressure of oxygen is what man depends upon for life At 47 000 feet the barometric pressure is 100 mm of mercury and 47 mm of water vapor accumulates in inspired air before it reaches the alveoli of the lungs This must be deducted from the atmospheric pressure This leaves us 53 mm of available atmospheric pressure in the alveoli From this must also be deducted the carbon dioxide pressure There is no known method of breathing supplementary oxygen that prevents dilution by outside air and hence this less than 53 mm of possible O_2 pressure is reduced still further Forty mm of pressure in the alveoli is about the minimum at which man can exist for more than a few minutes Even then the blood is somewhat venous and the individual suffering from extreme oxygen want In addition the carbon dioxide pressure has fallen due to the increased ventilation of the lungs and this fall in carbon dioxide pressure decreases the dissociation of oxygen from the hemoglobin in the tissues Hence somewhere about 47 000 feet is the absolute limit for man even when breathing pure oxygen

From 10 000 feet to about 34 000 feet the use of supplementary oxygen in gradually increasing percentages will restore the aviator to sea level conditions At 33 000 feet he needs 100 per cent oxygen From then on up even with 100 per cent he again suffers from increasing oxygen want due to the diminished partial pressure of oxygen available It has been estimated that a man at a little over 40 000 feet breathing pure oxygen is in the same condition as a man at 18 000 feet without oxygen and somewhere around 47 000 feet he will die even though breathing 100 per cent oxygen

The flights in a balloon to the stratosphere by Piccard were accomplished by the observers being sealed in a metal ball in which the atmospheric pressure was kept up to a point compatible with life In flights of airplanes to this level the cabin was sealed hermetically and the pressure within the cabin artificially kept at a level compatible with life as well as a means provided for elimination of carbon dioxide as an excess of the latter is as bad as too little In pressure cabins the atmosphere is

kept at a level of 8 000 feet At altitudes of 40 000 or more feet if a leak ensues not only will acute oxygen want develop but unconsciousness will ensue rapidly and air "bends are apt to occur

On repeated flights to high altitudes above 10 000 feet oxygen should be used On any flight above 12 000 feet it should be used No flyer can perform his mission safely and efficiently at high altitudes without oxygen Barach states that impairment of reason memory and judgment takes place at altitudes as low as 12 000 feet[4]

Gaseous oxygen is the type commonly used It is fed to the pilot through a face mask of the B L B or similar type[7]

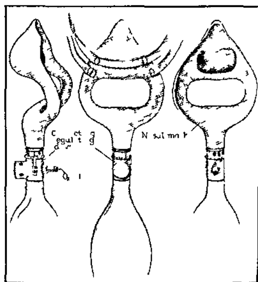


FIG 10 The Boothby Lovelace Bulbullian (B L B) nasal oxygen mask (Courtesy Walter M Boothby and the Bruce Publishing Company)

AERO EMBOLISM AND EMPHYSEMA

At levels above 25 000 feet we encounter not only the effects of oxygen want but the effects of greatly lowered barometric pressure With rapid ascents through these high altitudes nitrogen is given off in gaseous form into the blood and tissues If the gaseous bubbles are in the blood they may form air emboli If they penetrate the tissues emphysema results The condition is the same as what has long been known as caisson disease or the bends The condition may be sufficient to cause discomfort actual distress or even total disability It occurs frequently

at levels between 30 000 and 40 000 feet Paralysis may result from air embolism to the spinal cord

Behnke[1] states that bends will develop between 25 000 and 28 000 feet without preoxygenation By this is meant breathing 100 per cent oxygen prior to the take off He found that with 45 minutes of pre oxygenation *bends did not develop until 30 000 feet were reached* with 90 minutes not until 34 000 feet with three hours not until 37 000 feet and with five hours not until 40 0000 feet He found also that using a mixture of oxygen and helium instead of pure oxygen shortened the time necessary to accomplish the same end For example 90 minutes of breathing the oxygen helium mixture was equivalent to 5 hours of pure oxygen Behnke found also that the younger group of pilots was far less susceptible to aero embolism than the older group He recommends pre flight tests for selection of those to do high altitude flying

Effects of High Speed

High speed in flying is becoming more and more common Passenger airplanes now frequently travel at 200 or more miles per hour Such a speed however is not particularly dangerous The speed planes however flying 300 or more miles per hour are a different matter Dive bombing in which the plane attains 500 miles per hour before the pull out is serious

Straight ahead speeds are far less dangerous than speed on turns because the acceleration is gradual and there is no change of direction In turning however there is danger of unconsciousness Even turning sharply at 200 miles an hour may cause everything to become blotted out for the flyer This usually is transitory and the flyer promptly recovers Sometimes the blotting out persists for several seconds One flyer who pulled his ship up in a test at 190 miles an hour states that every thing remained black for 45 seconds One Army officer did not fully recover his vision for several hours Carsaux[14] in experiments on dogs rotated the animals on a wheel at speeds varying from four to six turns per second Some of the dogs showed actual brain damage due to the pressure of the brain against the skull Autopsies showed an anemia of the brain and an engorgement of the vessels of the abdominal area

In dive bombing the pull of centrifugal force on change of direction at about 500 miles per hour amounts to 5 or more G s 1 G is equal to the pull of gravity namely the pull to which we are accustomed and which keeps us from falling off the earth When this pull is increased we feel the effects At a pull of 5 G s muscular power is overcome and

breathing becomes almost impossible The blood is drained away from the upper part of the body and unconsciousness ensues There may be according to some a factor of vasomotor relaxation in addition to the pull of centrifugal force

The exact point of unconsciousness depends somewhat on individual tolerance but it occurs between 6 to 8 G s There is a fall in blood pressure in the upper half of the body and an increase in the lower half as would be expected Fulton[13] states that at 7 G s a man weighing 180 lbs would weigh 1 260 lbs the weight of the hydrostatic column of blood on the arterial side would be more than the heart could cope with and the venous blood would fail to return from below the cardiac level

All these remarks pertain to positive acceleration which is the common condition met in flying Negative accelerations are met in certain acrobatic manœuvres Here we find the reverse the blood being drawn to the upper part of the body with resulting seeing red instead of black, with cerebral congestion conjunctival and even cerebral hemorrhages being a possibility Armstrong states that at 4½ G the highest negative acceleration studied in man there is mental confusion persisting for several hours accompanied by severe throbbing headache The face is congested petechial hemorrhages result in the skin and conjunctive and subcutaneous ecchymoses may remain for hours or days

Prevention of the effects of positive accelerations may be obtained in part by (1) the pilot wearing an inflatable abdominal belt exerting sufficient pressure to prevent pulling of the blood to the lower half of the body (2) placing the pilot in a crouching posture so as to bring the pull of centrifugal force more transversely rather than from head to feet and (3) by having him yell at the top of his lungs thereby fixing his diaphragm and causing some cerebral congestion

Effects of Cold and Wind

Considerable work has been done recently on the effects of cold in flying We know that during the first mile of ascent the temperature falls 10° F in every 540 feet of ascent From 14 000 to 16 000 feet there is a fall of 1° F in every 360 feet of ascent From 23 000 to 29 000 feet there is a fall of 1° F in every 188 feet of ascent Above 35 000 feet is the zone of constant temperature −67° F below zero

Schneider[13] states that in flight cold increases by stages First there is a sensation of chilling a development of goose pimples and pallor if there is not sufficient protection the chilling accentuates there is a development of painful sensations the extremities become stiff followed by

numbness and a tendency to sleep The fall in temperature stimulates metabolism and therefore the demand for oxygen is increased a fact worthy of note at high altitudes where extremes of cold and low oxygen tension are encountered Heavy clothing is inadequate at very low temperatures and it further restricts free movement Armstrong states that at −40° F there is a loss of morale distraction acute physical suffering muscular sluggishness and incoördination with finally a tendency to stupor

The effects of wind in flying according to Aggazzotti[1] and Galeotti are such as to cause irregularity and acceleration of respiration and a diminution in alveolar carbon dioxide Strong winds may interfere with the entrance of air to the lungs hinder movements of the thorax and decrease lung ventilation Metabolism will be increased by the effect of wind in flying and this increases the demand for oxygen

With the use of cabin ships the effects of wind are less important than in open ships so far as the effect on the pilot is concerned Pinson and Benson[28] state that the final solution to the problem of maintaining body heat under the varied and extreme conditions encountered in flight is dependent to a great extent on future developments in airplane design In pressure cabin planes heating of the cabin with a provision for defrosting the windows may be the answer At present they recommend using the best features of the electrically heated suit with the use of insulative clothing of maximum bulkiness commensurate with normal personal comfort and efficiency

Blind Flying

This comes rather under the head of flying training than under aviation medicine Nevertheless the difficulties of blind flying are physiological and so a few words must be said on this subject By blind flying is meant flying without a horizon for guidance This occurs in fogs thick weather and above the clouds We have seen that equilibrium depends on several factors and one of these the most important in the pilot is vision Vision is of no use in blind flying Our other senses are unreliable and hence the flyer must depend on instruments to determine his position in space This sounds simple but is not because one s physical sensations are overpowering unless he has been specially trained

That vertigo results from spinning and turning is well known That this vertigo is not only confusing but causes false sensations of direction is not so well understood However that such is the case can be easily demonstrated by a Barany or other turning chair

breathing becomes almost impossible The blood is drained away from the upper part of the body and unconsciousness ensues There may be according to some a factor of vasomotor relaxation in addition to the pull of centrifugal force

The exact point of unconsciousness depends somewhat on individual tolerance but it occurs between 6 to 8 G s There is a fall in blood pressure in the upper half of the body and an increase in the lower half as would be expected Fulton[13] states that at 7 G s a man weighing 180 lbs would weigh 1 260 lbs the weight of the hydrostatic column of blood on the arterial side would be more than the heart could cope with and the venous blood would fail to return from below the cardiac level

All these remarks pertain to positive acceleration which is the common condition met in flying Negative accelerations are met in certain acrobatic manœuvres Here we find the reverse the blood being drawn to the upper part of the body with resulting seeing red instead of black' with cerebral congestion conjunctival and even cerebral hemorrhages being a possibility Armstrong states that at 4½ G the highest negative acceleration studied in man there is mental confusion persisting for several hours accompanied by severe throbbing headache The face is congested petechial hemorrhages result in the skin and conjunctivæ and subcutaneous ecchymoses may remain for hours or days

Prevention of the effects of positive accelerations may be obtained in part by (1) the pilot wearing an inflatable abdominal belt exerting sufficient pressure to prevent pulling of the blood to the lower half of the body (2) placing the pilot in a crouching posture so as to bring the pull of centrifugal force more transversely rather than from head to feet and (3) by having him yell at the top of his lungs thereby fixing his diaphragm and causing some cerebral congestion

Effects of Cold and Wind

Considerable work has been done recently on the effects of cold in flying We know that during the first mile of ascent the temperature falls 10° F in every 540 feet of ascent From 14 000 to 16 000 feet there is a fall of 1° F in every 360 feet of ascent From 23 000 to 29 000 feet there is a fall of 1° F in every 188 feet of ascent Above 35 000 feet is the zone of constant temperature −67° F below zero

Schneider[13] states that in flight cold increases by stages First there is a sensation of chilling a development of goose pimples and pallor if there is not sufficient protection the chilling accentuates there is a development of painful sensations the extremities become stiff followed by

For example if the applicant is turned to the right with his eyes closed say 10 times in 20 seconds he at first has a sensation of turning to the left then a sensation of turning to the right and if the turning rate then is slowed or stopped altogether he has the sensation of turning to the left If he opens his eyes the falsity of his sensations is apparent at once

The cause of these sensations is due to stimulations of the end organs of the vestibular branch of the eighth nerve in the semicircular canals The exact physiological phenomenon has been a source of great dispute among otologists but it is pretty generally agreed now that the cause is a change of tension in the fluid in these canals For our purposes however the exact cause is not important the fact that such sensations occur is the factor to be considered

The practical application of this to flying is the following If a pilot flying in a fog gets into a spin and then comes out of it he has the sensation of spinning in the opposite direction If he depends on this sensation he will correct for the supposed spin and this correction at once puts him into another spin This may keep up in a vicious circle until he crashes His only hope is to disregard his sensations and fly by instruments

Many flyers have in the past complained after blind flights from which fortunately they returned that their instruments were wrong and were disconcerting Without some such demonstration as has been outlined above it would be impossible to convince these flyers that their instruments were right and that they or their sensations actually were wrong

To follow one s instruments is difficult without special training because these erroneous sensations one receives are overpowering until he has been trained to disregard them In this connection it is interesting to note that Ocker[a] found trained flyers were unable to fly a course by instruments without re education even though they realize its necessity They had been flying too long by feel to be able suddenly to disregard their sensations On the other hand they found that an untrained or rather a very slightly trained flyer could do fairly well because he had nothing to unlearn

Military pilots are now trained in blind flying and all air line transport companies also train their flyers in it The instruments used include not only an altitude indicator an air speed indicator tachometer turn and bank indicator a gyro compass as well as a magnetic compass but an instrument giving an artificial horizon such as the flight integrator of Ocker and Crane[a] or a gyro horizon



FIG 11 Apparatus for demonstrating to a pilot the fal ity of hi ensations after turning The side of the camera has been removed to show the interior The scheme was fr t suggested by Colonel D A Myers U S Army (Ret) Apparatus perfected by Colonel W C Ocker U S Army

of motion hypersensitiveness annoyance by bright light little noises etc restlessness

Bainbridge[3] considers staleness as nothing more or less than "effort syndrome" It results from severe exertion or in the course of training and the circulatory and respiratory changes which occur normally are increased He further believes that the contractile power of the heart is diminished and that oxygen want plays a part in functioning of the muscles and nervous system The changes in pulse respiration and blood pressure result from an insufficient supply of oxygen

Effort syndrome or neurocirculatory asthenia was described first by Lewis[18] He describes four groups of cases These are (1) constitutional or hereditary group (2) a group due to exposure and mental or physical strain (3) convalescent group (4) toxic group

The symptoms are in the order of importance breathlessness brought on by exertion the rate of breathing being markedly increased by exercise pain usually this is exaggerated by exercise exhaustion even mild cases show fatigue on moderate exertion and palpitation is common giddiness is more or less constant and is associated with change of posture and effort fainting may occur other symptoms are headache lassitude irritability sleeplessness inability to fix attention coldness of the hands and feet sweating particularly of the hands feet and axillæ

The physical signs are increased heart rate and particularly an exaggerated response of the heart to exercise with a slow return of the pulse after exercise There are exaggerated responses of the blood pressure although frequently we find that upon change of posture the blood pressure falls rather than rises The apex beat may be diffuse and the heart sounds accentuated Functional systolic murmurs may be present There is an exaggeration of the deep reflexes and coarse tremor of the hands and tongue The symptoms of an individual case may be anything from breathlessness up to a definite picture presenting the above symptoms The stale flyer presents much the same picture The flight surgeon should be continually on the watch for the development of this condition It must be caught in its incipiency for if it is allowed to develop not only may a serious accident occur but recovery becomes prolonged and uncertain Staleness may be prevented by maintaining a condition of physical fitness Exercise and proper rest are the essential factors in this program

Bainbridge[3] states that training develops the skeletal muscles and also the heart A person in training shows a slower pulse lower blood pressure and a lessened minute volume of the heart The heart output is greater per beat and the oxygen carrying power of the blood has a greater

CARE OF THE FLYER

Selection of the flyer is only part of the problem important though it is Once selected the pilot must be maintained in at least as good condition as he was at the time of his selection This requires frequent observation In the Army and Navy flyers are all under the constant supervision of a trained flight surgeon Both services require the flyer to check out daily through the flight surgeon before flying This is the ideal arrangement The flight surgeon becomes thoroughly acquainted with his flyers and knows their habits and weaknesses He knows which flyer needs more supervision which takes good care of himself Aside from the required semi annual examinations frequent checks of certain physical points are made as developments warrant In the service whenever a student flyer begins to fall off in his flying makes poor landings or what not, he is sent to the flight surgeon for an overhaul

Fatigue — Flying is fatiguing and too much of it results in staleness or neurocirculatory asthenia Not only too much flying will bring on this condition but too little exercise too little recreation or too much dissipation likewise will do it

Schneider[30, 31] has defined fatigue as a progressive flagging of efficiency together with a subject sensation of the loss of control of the muscles Physiological activity becomes lowered and the ability to work is diminished When a person engages in normal activity it is a natural result that fatigue ensues However this fatigue should be relieved completely by a night s sleep When it is not relieved and the activity responsible for it continued there will be an accumulative fatigue which eventually burns up the reserve and we have staleness resulting

Staleness — Schneider[31] has defined the various types of staleness as follows (1) Cardiorespiratory — Pulse increase in rate poor in volume and low in tension There is distress on slight exertion accompanied by an inordinate rise in pulse rate and prolonged time of return of the pulse after exercise breathing shallow and rapid extremities poor in color cyanotic and cold (2) Nervous type — Poor muscular control of balancing movements fine tremors of the hands eyelids and tongue apprehensive starts with sudden sensory experiences disturbed sleep loss of sleep nightmare (3) Muscular type — Tenderness of the muscles with loss of tone flabbiness loss in power which may be marked or slight These symptoms may be confused with rheumatism (4) Staleness may be brought about also by disorders of digestion characterized by removal of normal inhibitions i e reponse to sensory stimuli by excess

or over unfavorable territory This they feel forms the basis of emotional stress They state Our findings lead us to believe that there is possibly a drain on the suprarenals during flying whether it is physical or mental It might then follow that an exhausted suprarenal gland may affect the sympathetic nervous system in such a way as to reduce its tonicity Further this drain or exhaustion of the adrenals is probably the cause of fatigue with its associated hypotension Our opinion is that due to prolonged emotional stress the sympathetic nervous system stimulates adrenalin secretion which causes a decrease in the liver and muscle glycogen Exhaustion of the liver glycogen calls forth the manufacture of carbohydrate from protein and possibly fat resulting in the tearing down of tissues This anabolism produces an increase in the acids and these acids in turn stimulate the respiratory centers to cause increased pulmonary ventilation This is necessary to keep pace with the demand for oxygen Our blood sugar findings are low This denotes increased sugar consumption and as the energy is needed the demand becomes greater on the adrenals until we have a depletion and adrenalemia with resulting fatigue and hypotension

Padden[27] reports that irregular hours and excessive flying affect ocular muscle balance early He lays great stress on goggles and states that many difficulties are encountered due to optically imperfect lenses in the goggles He recommends frequent checking of goggles to protect the eyes of the flyer

Flyers are particularly prone to develop gastrointestinal upsets probably due partly to emotional stress and partly to the irregular hours and irregular meals One transport operator had 16 per cent of his pilot personnel develop acute appendicitis in 13 months All these cases were operated on and in all instances the attack came on from within 5 minutes to 2 hours of takeoff and in one pilot while flying his run Gastric ulcer is not infrequent and probably due to the same causes

Diseases of the upper respiratory passages due to exposure to cold and fatigue middle ear troubles particularly in altitude flights are common

All these factors show the need for medical supervision One flight surgeon reported that the effect of irregular schedules meals sleep and recreation showed by frequent minor accidents poor morale among pilots staleness and a marked decrease in general physical fitness Flying then causes fatigue and this may cause various physical ailments and eventually may develop into staleness a falling off in flying ability occurs and nervous instability results

The flight surgeon must detect such conditions early and take the necessary measures to prevent a state developing that will necessitate

coefficient of utilization Movements are better coordinated and there is a better economy of effort

The development of staleness results in a dislike of flying and a loss of flying efficiency Poor landings the loss of the feel of the ship neglect of details such as attention to instruments position of stabilizer neglect of altitude adjustment and incorrect computations of gas expenditures may result Poor judgment becomes common and the flyer does not make prompt decisions

Staleness is insidious in its development and frequent medical supervision is important In civilian flying constant medical supervision is not practicable Its importance however is considered so great that several air lines in the United States employ flight surgeons to check the physical condition of their pilots monthly

Wright[36] feels that a pre employment examination is essential in order that the pilots can be certified for their positions not only in regard to their present state of health and efficiency but to prognosticate their adaptability to conditions their reliability and stamina He feels that the Schneider index is an excellent method of keeping track of the flyers physical efficiency This test was devised by Schneider[30] primarily for use in following the physical condition of aviators It will be described later in the chapter

Miller and Ginsberg[4] studied metabolic and serological changes in flight fatigue in a group of pilots They found hypotension was common after flight and wondered whether or not this was an evidence of fatigue They made determinations of basal metabolic rate blood sugar creatinine and non protein nitrogen before and after flight in a group of 15 pilots They also took Schneider tests and flarimeter tests on the same group

A brief summary of the work follows Fifteen veteran pilots have been studied Forty six and six tenths per cent of these pilots show a lower basal metabolic rate after flying in comparison to the basal metabolic rate found after resting Blood sugar values were low Identical values were almost always found for blood sugar after flying and after rest Creatinine determinations show no change Non protein nitrogen determinations show that forty six and six tenths per cent give higher values after rest but this group is not related to the group showing higher basal metabolic rates after flying The Schneider index permits us to conclude that a pilot has a more efficient neurocirculatory mechanism after rest They suggested that the hypotension may be a sign of physical fatigue caused by drain or exhaustion of the adrenals Flying causes fear in the novice and this gradually becomes more or less repressed into the unconscious Fatigue is induced more quickly by flying in bad weather

3 The subject then rises and stands for two minutes to allow the pulse to assume a uniform rate When two consecutive 15 second counts are the same multiply by 4 and record This is the normal standing rate
4 Standing pulse minus the reclining pulse gives the increase on standing
5 The systolic pressure is taken as before and recorded
6 Timed by a stopwatch the subject steps upon a chair 18½ inches high five times in 15 seconds To make this uniform the subject stand with one foot on the chair at the count one This foot remains on the chair and is not brought to the floor again until count five At each count he brings the other foot on the chair and at the count down replaces it on the floor This should be timed accurately so that at the 15 second mark on the stopwatch both feet are on the floor
7 Start counting the pulse immediately at the 15 second mark on the stopwatch and count for 15 seconds Multiply by 4 and record
8 Continue to take pulse in 15 second counts until the rate has returned to normal standing rate Note the number of seconds it takes for this return and record In computing this return count from the end of the 15 second of exercise to the beginning of the first normal 15 second pulse count If the pulse has not returned to normal at the end of 2 minutes record the number of beats above normal and discontinue counting
9 Check up points and enter final rating
10 Enter history of case including amount of sleep amount of smoking kind of work (outdoor or indoor active or sedentary etc) time since last meal any personal worries or any pathological condition which might affect the condition of the subject The test should not be made within 2 hours after a meal and the habits of the individual must be taken into consideration

Roughly an index of 14 to 18 is excellent 10 to 13 very good 7 to 9 borderline below 7 unsatisfactory

Scott[3] by means of systematic exercise over a period of one month improved the average index of a group of flyers The results before the exercise was started were 20 per cent 14 or above 60 per cent 8 to 13 and 20 per cent 7 or less At the end of the month the results were 80 per cent 14 or above 10 per cent 8 to 13 and 10 per cent 7 or less

As a gauge of condition in athletes flyers and those subjected to constant mental strain whose condition may be checked from time to time it is probably the most satisfactory test yet devised

Flying Time for Pilots

This is a much mooted question but as flying is fatiguing and apt to induce staleness if overindulged in a limit in the amount of flying a man should do must be set in the interest of safety and efficiency The Army considers 100 hours per month as the limit and its pilots are under constant medical supervision Taken as a whole peace time flying in the Army with its associated military duties may be compared with transport flying from the physical standpoint

complete removal from flying status or that will result in accidents Careful selection regular exercise avoidance of too much flying adequate rest and recreation will prevent staleness Laboratory examinations should play a part in the supervision of pilots as pointed out by Tillisch and Lovelace[31] They found 73 of 103 pilots had defects which did or could affect their health Many of these defects would have gone unrecognized in an ordinary physical examination

The Army Flight Surgeon s Handbook[11] recommends that the limitation of flying hours as given later under Flying time should be adhered to The Army also feels that on completion of a mission crews should be taken 3 to 5 miles away from the airdrome for rest and sleep Attention is called to the fact that mild degrees of anoxia increase fatigue Strict oxygen discipline should be insisted upon New personnel joining operational units should be watched carefully as inadequacies are apt to crop up early It is advised that flying stress once developed should be treated only in a hospital They consider flying stress is ' infectious

McFarland[27] in an excellent treatise on fatigue in aircraft pilots shows that a pilot whose muscular activity in flight is limited could hardly exhaust the energy reserves sufficiently to explain the fatigue and exhaustion often observed in airmen He ascribes the acute and chronic pilot fatigue and exhaustion to psychological factors such as emotional stress regardless of whether it is related to adverse flying conditions fear of accident economic and social insecurity and unhappy marital adjustments He also considers lack of exercise reduced oxygen tension in high altitude flights poor selection of food and excessive use of tobacco and alcohol as contributing factors to fatigue Other variable contributing factors are noise, vibration poor illumination glare, static from the radio and poor regulation of ventilation and temperature

Physical fitness is more important in flying than in any other occupation The necessity of constant medical supervision or as near constant as practicable cannot be too strongly emphasized

The technique of the Schneider test already mentioned is described below

DIRECTIONS FOR PROCEDURE IN THE CIRCULATORY EFFICIENCY TEST (SCHNEIDER INDEX)[30]

Preliminary Subject reclines for five minutes

1 Heart rate is counted for 20 seconds When two consecutive 20 second counts are the same this is multiplied by 3 and recorded
2 The systolic pressure is taken by auscultation and recorded Take two or three readings to be certain

Air line flying may be divided into day and night flying To deal first with the former it is believed that the air line regulations which in peace time limit the total flying of any pilot to 85 hours per month is reasonable Poor terrain heavy passenger loads poor average weather conditions and lack of a co pilot should reduce the maximum Good terrain the presence of a co pilot and good average weather conditions may increase it somewhat perhaps to 100 hours Or in the case of repeated short flights under good conditions perhaps slightly more

As to night flying this is admittedly more hazardous and more of a strain With the same factors acting in modification a limit of 60 to 75 hours per month is desirable

In advancing any limits however it should be assumed that the pilot obtains sufficient sleep each day under restful conditions to give the necessary recuperation from exhaustion and place him in condition to resume flying

The commercial pilot should have one or more days a week off from flying Under good flying conditions one day may be sufficient but under more trying conditions every third or fourth day should be taken off In addition the pilot should have from three to four weeks a year off Whether one vacation of four weeks is better than two vacations of two weeks each is perhaps still open to argument but that it should not be subdivided more than that is generally agreed by medical men

Because of the war limitation of flying hours has been removed and already many pilots have complained of marked fatigue inadequate rest periods and the excellent record for safety made during the past several years by the air lines of the United States will be in grave danger

In military operations it is important to space operations for the pilot as evenly as possible Ninety to 110 operational hours in six weeks has been recommended for fighter pilots and 1 0 to 139 hours of operational flying for bombers in three months Leaves should be given then followed by a period of flying not involving operations before return to operational duty

The Army feels that 7 days is as long a leave as should be given but that this should be given at stated intervals One half a day off should be given every 3 or 4 days 48 hours every 2 weeks and 7 days at the end of the operational limit

AIR SICKNESS

Sea sickness has been known ever since man took to the sea and air sickness became fairly common after flying became prevalent The cause

TABLE OF POINTS FOR GRADING CARDIOVASCULAR CHANGES IN THE SCHNEIDER INDEX

A Reclining pulse rate		B Pulse rate increases on standing				
Rate	Points	0–10 beats points	11–18 beats points	19–26 beats points	27–34 beats points	35–42 beats points
50–60	3	3	3	2	1	0
61–70	3	3	[illegible]	1	0	–1
71–80	[illegible]	3	[illegible]	0	–1	[illegible]
81–90	1	2	1	–1	–2	–3
91–100	0	1	0	[illegible]	–3	–3
101–110	–1	0	–1	–3	–3	–3

C Standing pulse rate		D Pulse rate increase immediately after exercise				
Rate	Points	0–10 beats points	11–20 beats points	21–30 beats points	31–40 beats points	41–50 beats points
60–70	3	3	3	2	1	0
71–80	3	3	[illegible]	1	0	0
81–90	2	3	2	1	0	–1
91–100	1	[illegible]	1	0	–1	–2
101–110	1	1	0	–1	[illegible]	–3
111–120	0	1	–1	–2	–3	–3
121–130	0	0	[illegible]	–3	–3	–3
131–140	1	0	–3	–3	–3	–3

E Return of pulse rate to standing normal after exercise		F Systolic pressure standing compared with reclining	
Second	Points	Change in millimeters	Points
0–30	3	Rise of 8 or more	3
31–60	2	Rise of 2–7	2
61–90	1	No rise	1
91–120	0	Fall of 2–5	0
After 120 2–10 beats above normal	–1	Fall of 6 or more	–1
After 120 11–30 beats above normal	–2		

The test must be performed accurately and painstakingly Also one index is not of much value Several should be had in order to afford a basis for comparison

The frequency of air sickness is disputed Some authorities claim it occurs in 5 per cent of passengers but this probably is too high A great deal of course depends on flying conditions On a smooth day only rarely is a person air sick while on a rough day more are sick Tuttle[34] found in a survey of the United Air Line flights that the rate of air sickness was only 3 per 100 He classified all discomfort in air line planes as follows

Air sickness	0 33%
Nervousness	0 09%
Oxygen want	0 08%
Ear trouble	0 05%
All others	0 05%
Total	0 60%

Conclusion

Aviation Medicine therefore has an important field By means of it the public is assured of safety in flying so far as the physical side is concerned It includes a broad knowledge of medicine and psychology and a personality in the flight surgeon that inspires confidence and respect

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of air sickness is the same as the cause of sea sickness namely unaccustomed motion with overstimulation of the vestibular mechanism We have other similar forms of sickness namely train sickness swing sickness etc all of which are due to the same cause

The airplane moving through a rather unstable medium is similar to a ship plowing through pitching seas The air is smooth on some days and rough on others On windy or gusty days the air is rough Likewise on days on which there has been a sudden drop in temperature the air is rough and bumpy due to the fact that the air is not uniformly cooled and we meet warm and cold currents of air alternately The air usually is bumpy over mountains and in crossing bodies of water from the land This unaccustomed motion stimulating our motion sensing apparatus causes a certain amount of vertigo and nausea

Some people are more prone to air sickness than others just as is the case with sea sickness The nervous high strung type of individual is more apt to be air sick than the phlegmatic type Fear often acts as an exciting cause for air sickness There is therefore a psychological factor in air sickness aside from the physical factor The person who is car sick or sea sick probably will be air sick also

There are certain measures to be carried out as a prophylactic The passenger for pilots are rarely air sick should avoid eating rich or heavy food before flying He should be instructed to swallow frequently as this keeps his Eustachian tubes open and prevents pain developing from retracted ear drums on sudden change of altitude Chewing gum facilitates keeping the Eustachian tubes open The passenger also should have his attention diverted as much as possible If he can be encouraged to follow a map it takes his mind off himself and prevents fear If he actually becomes sick he should be made to go to the wash room to avoid upsetting other passengers An alkaline effervescent drink is recommended by Wright[36] as a cure for nausea in the air If food is taken toast plain crackers or an apple are less upsetting to an air sick passenger than heavy food or liquid except for an alkaline drink

Both Padden[27] and Wright[36] recommend a grain or two of amytal for a nauseated passenger Wright states such a passenger often will drop off to sleep and awake feeling refreshed enough to enjoy the remainder of the trip

Just as the person used to the sea is less apt to be sea sick than one who rarely sails so the one who flies frequently is less apt to be air sick Pilots rarely are air sick partly because they are so used to flying and partly because they are busy and have no time to think about themselves

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CHAPTER XV

THE RATIONALE OF CLINICAL DIAGNOSIS

(*Medical Logic*)

By LEWELLYS F BARKER

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IN making a diagnostic survey we recognize the existence or absence, of ' disease in a person through determining the presence or absence of certain symptoms or signs drawing inferences from our findings reasoning out the implications of these inferences testing them for their validity and finally arriving at the concluding belief that ' disease " has been identified or that the person is ' healthy It is mainly the logical basis and the technique of the process that will be discussed in the present article

DEVELOPMENT OF CLINICAL DIAGNOSIS

During the long period in which human beings have lived enjoyed and suffered there has gradually grown up a body of opinions and beliefs regarding health and disease At all times animals and human beings have been subject to accidents and diseases that entail suffering

or disability A human being who suffers pain or who is conscious of disability desires and seeks, relief Other human beings who see him suffer have their interest and sympathy aroused and desire to help him or to find someone who can help him Even among the primitive healers who called upon the gods to cure, or made use of magic arts and enchantments, there must have been a recognition of different kinds of suffering and of the need of a corresponding variety of remedial measures Among these healers, too, there doubtless early arose, as incentive to discrimination, in addition to the desire to help and the desire for knowledge the desire to be successful for the sake of livelihood, power, prestige, and other personal rewards In the effort to satisfy these desires partly private partly social the art of diagnosis had its crude empirical beginnings Listening to the complaints of those who suffered watching their behavior, comparing the observations made on a given case with those made on others earlier in their experience, primitive healers gradually acquired experience and handed down their observations, opinions beliefs, and customs to their successors (medical tradition)

The striking character of certain illnesses and accidents unquestionably helped to determine the order of development of medical observation and opinion Wounds, hemorrhages fractures and dislocations large tumors phlegmons convulsions paralyses chills fevers, anasarca deliria violent pains blindness, deafness jaundice, persistent vomiting madness melancholy and other gross manifestations doubtless earliest attracted attention, an acquaintance with these that permitted him to recognize them when he met them constituted the diagnostic knowledge of the ancient practitioner It is easy then to understand why in earlier times external medicine should have developed before internal medicine and why the observation of the natural course of disease should have yielded important facts that bore upon prognosis long before a therapy that could lay any claim to rationality could be applied

The study of the natural course of disease and of prognosis was doubtless an inspiration to further diagnostic discrimination and resulted in the general growth of diagnostic knowledge The course and the outcome were so different in different cases of hemorrhage of fever and of paralysis for example that curiosity must early have been stimulated to seek explanations by attempting an analysis of the different kinds of hemorrhage of fever and of paralysis The primitive descriptions of disease were perforce vague and indefinite The class names that were first used in diagnosis were names of what we now call symptoms and signs The groupings that the earlier diagnosticians

made use of were probably the best that could be selected for the purposes of their time but we can be sure that then as now there were only a few who recognized that groupings are conceptual and that they must be changed when the purposes for which they are wanted change The rank and file are at all times prone to accept classes and class names as given facts that need no further investigation The value of a class name is to assemble (for convenience in making general statements) individuals that have points of resemblance or common attributes despite the fact that they also differ from one another the class name stands for unity in spite of difference When for example diagnosticians assembled a group of cases under the class name paralysis they sometimes forgot that the differences between one member of the class and other members of that class might for certain purposes be more important than the resemblances Thus a gumma pressing on the thoracic portion of the spinal cord causes paralysis a metastatic carcinoma in the same region causes paralysis For the purposes of description the class name paralysis has its value for both instances for purposes of prognosis and therapy other class names (syphilis and cancer) are more important In other words in assigning an individual to a class the value of the assignation depends upon the aim or purpose we have in view We have gradually to find out the 'degrees of generality that exist for one class possesses higher generality than another if it includes not only that other but also more The older logicians recognized these scales of generality and arranged tables of higher classes (general) and lower classes (special) in order—the so called tree of division or classification (e g Porphyry s tree) And advance in diagnosis has resulted from discovering specific differences (differentiae) between members of general classes made for certain purposes and discovering features that make assignation to other classes that we create for other purposes more important By examining closely the members of a class for portions that for some clearly seen purpose differ essentially from one another diagnostic thought moves ever towards clearer definition This movement from vagueness towards definiteness is on the one hand the effect on the other the cause of each advance in the growth of diagnostic knowledge

Now it is this movement of diagnostic thought impelled by the desire for more effective treatment based upon more accurate and ever more definite knowledge that accounts for the growth of the medical sciences as a whole and for the subdivision of diagnosis itself into three parts (pure science applied science and art) In order that diagnosis may become something more than merely regional and external a knowledge of the interior of the body and its development a knowledge of the

mind and its development and a knowledge of the environment of the body and mind including a knowledge of the modes of interpenetration of associated minds become important Anatomy, physiology, pathology and psychology are the sons and daughters of diagnosis, children that in turn contribute lavishly to the parental larder Diagnosis gradually became internal as well as external, organal histological, cytological, and chemical as well as regional, functional and dynamic as well as structural and static, psychic as well as somatic, social and situational as well as personal, etiological and pathogenetic as well as symptomatic and descriptive Diagnosis has become partly a pure science based upon data derived from a large number of subsidiary sciences, partly an applied science in which the utilities of the truths of the pure science are perceived and the necessary adjustments for realizing them are made, and partly an art in the exercise of which practitioners employ more or less skillfully the inventions that the applied science affords

The Position and the Relationships of the Science of Clinical Diagnosis

The meaning of diagnosis has, during the centuries, become gradually enlarged The term "diagnosis" came to us through Latin from the Greek *dia-*, through or thorough, and *gignōsko* recognize As applied to day it is of course attached to a far more complex subject than could have been anticipated by those who first used the name Through the development referred to above a development that is going on in our time more rapidly than ever before a pure science an applied science and an art of diagnosis may be said to have come into existence, for we now possess (1) laws and principles that hold in diagnosis ("pure" or 'theoretical' diagnostic science), (2) perceptions of the possibilities of utility and inventions through which the principles are applied (practical,' or 'applied," diagnostic science) and (3) skill and experience in employing these inventions in practice (diagnostic art)

The ' pure" science of medical diagnosis treats of the phenomena and laws of disease explains the processes by which pathological phenomena occur tracing each phenomenon back through a series of antecedent conditions and inquires into the anatomical physiological biological, chemical physical psychological, and social causes of disease states This ' pure ' science of diagnosis like every other ' pure" science is interested in facts and their regular occurrence It reasons about the facts and discovers 'truth" but it rests upon faith namely 'faith that causation is universal" faith that "all effects have causes

and all causes have effects,' and faith that beneficial results will follow the discovery of truth'

The progress of any science is irregular and more or less paroxysmal but the general methods used for making progress are the same for all the sciences Progress in the science of diagnosis results from the work of a huge army of clinical and laboratory investigators each of whom has his individual peculiarities, has had his own special training and lives and works in his own particular environment It is not strange therefore that even men who are trying to solve the same problem should approach it in different ways should use different methods and should attain to somewhat different results Still the general method employed by all serious scientific research workers is the same A problem is set, a special technique suited to the particular purposes of the investigator is constructed observations and experiments are made the results are recorded If these results prove to be important they and the methods by which they have been obtained are published Other workers noticing the publication try to verify or to disprove the results using other similar materials but working by somewhat different methods in a different environment with a background of a different natural endowment and a different past experience They criticize and are led through their criticisms to make further observations and experiments All of the earlier results may be disproved or all of them may be verified more often some of the earlier results stand the crucial test and come to be admitted as truths by everybody whereas others of the results fail to stand the test and are rejected Gradually the tested and accepted results in connection with special problems in a number of circumscribed fields make a considerable mass and attract the attention of some worker with a synthesizing mind who coordinates the new results in comprehensive papers Later the results thus coördinated get into textbooks and the knowledge is made widely accessible the achievements of the relatively few workers in each circumscribed field can thus be appropriated by the many who are distributed over the whole area of medical research and medical practice Thus though advances in diagnosis may have been made by fits and starts the forward strides have been due to the application of the method of science

The science of medical diagnosis or science of the thorough recognition of disease is like every other true science a domain in which phenomena occur in regular order as the effects of natural or efficient causes such that a knowledge of the causes renders it possible to predict the effects In the last analysis the causes are natural ' forces they obey the Newtonian laws of motion The word law in science implies uniformity of movement In the sciences of mechanics astronomy

and physics, the phenomena can be, in large measure reduced to exact measurement and in them the "theory of units" (mass space, time) is easily applicable In the more complex sciences, the phenomena cannot yet be reduced to exact measurement except to a limited extent We *believe* however, that exact laws do prevail in medical science as well as in all natural domains, though our knowledge of these laws is as yet exceedingly imperfect It is "faith in the order of the universe" belief that laws are uniform and invariable in the fields of life, mind and society (as well as in other cosmic fields) that makes the sciences of biology, psychology, sociology, and medicine possible Social psychic and biotic phenomena are exceedingly complex, but study of them by exact methods reveals the existence of uniformities among them They occur in order They are subject to law just as rigorously as are the phenomena of chemistry and physics To discover the laws that health phenomena and disease phenomena obey, we must use the method of science, the method that has revealed to the physicist the laws to which heat light, electricity and magnetism conform The diagnostician must know in order that he may accurately predict and successfully control

A word may be said as to the place of diagnosis and of the other medical sciences in the classifications of all the general and special sciences that have been attempted The fundamental sciences as they have been arranged serially (and more or less genetically) are astronomy physics chemistry biology psychology, and sociology As complexity increases in the series the degree to which the phenomena can be exactly determined what Comte called the "positivity" decreases Comte made each of these coordinate fundamental sciences stand at the head of a hierarchy of sciences that can be arranged in a logical or synoptical order It is obvious that, if we adopted such a classification the natural place for the sciences of medicine would, like those of technology be within the hierarchy of which sociology is the head* Properly to understand the complex and less exact clinical science of diagnosis a comprehensive grasp (but not necessarily a mastery of the details) of all the simpler and more exact sciences (physiological biological chemical etc) below it is necessary Classifications of the sciences imperfect as they are do help us to understand the manifold relations of our own science and give useful pedagogic hints for the most suitable arrangement of curricula

To understand just what diagnosis is and what it is not it is necessary to determine its boundaries to differentiate it clearly from other

* No classification of the sciences as a whole can be regarded as entirely satisfactory A very good attempt at a more elaborate classification than the simple one given by Comte is that of Karl Pearson See his Grammar of Science 2 d ed 1900

sciences and especially perhaps from those to which it is most closely related The view or theory of the relations of the subject to other subjects and to the known world in general as distinguished from the view or theory of it as isolated or in itself ' has been given as a definition of the philosophy of a subject as distinguished from its science Though the distinction drawn between science and philosophy is now less sharp than that formerly drawn there is something to be gained by considering separately the philosophy of a science in the sense mentioned above namely its relationships and the definite delimitation of its field

Relations of Diagnosis and Physics

Of all the natural sciences to which clinical diagnosis is related none is more fundamental than the science of *physics* Under physics are grouped the subjects (excluding chemistry and biology) that treat of the properties of matter and energy and of the action of the different forms of energy on matter The conceptions of matter and energy of mass and motion and of space and time dealt with by physics lie at the basis of the scientific analysis of all natural phenomena including those that we deal with in diagnosis

The laws of dynamics which deal with the action of force on bodies whether at rest or in motion hold for the processes that go on within the human body which the diagnostician studies The prospective student of diagnosis who in his early education gains some acquaintance with theoretical mechanics not only acquires conceptions that aid him in the understanding of the problems of the pre clinical and clinical medical sciences but also through dealing with these ideal representations secures a training in abstract thought that should be helpful to him in the whole of his subsequent career The methods and principles of applied mechanics the subject that deals with the theory of tructures and with the theory of machines are likely as the medical sciences grow to be ever more applicable to the solution of problems connected with the structures and mechanisms of the human machine

That the study of the physics of heat light sound electricity and magnetism tand in intimate relation to the study of the functions of the human body in both normal and abnormal conditions goes without saying The diagnostician could not view intelligently the phenomena of fever and of metabolism if he were unacquainted with the effects produced by heat on material bodies with the laws of transference of heat and with the laws that govern transformation of heat into other kinds of energy Thermometry and calorimetry are simple and direct applications of physics to clinical diagnosis And how unsatisfactory

would be the work of the general as well as of the ophthalmic diagnostician who had not studied the physics of light, the laws of its rectilinear propagation of its reflection and of its refraction and the relations of light to the phenomena of vision and of color perception! In the construction of instruments of precision for diagnostic work, applied optics has made a very great contribution To recall this fact vividly to mind I need refer only to the microscope, the polariscope, the photographic camera, the ophthalmoscope the speculum, the cystoscope, the bronchoscope the sigmoidoscope, and the refractometer, and the uses to which they have been put in clinical diagnosis The manifold applications of mirrors and lenses of different sorts in clinical diagnosis nowadays are contributions of optics that command the gratitude of every worker in the field of clinical diagnosis Almost as important, too are the applications of the physics of sound to the work of clinical inquiry The art of auscultation in physical diagnosis can be practiced only inefficiently by one who is ignorant of the physical phenomena that correspond to the loudness, the pitch, and the quality of sounds Instruments of precision like the stethoscope the microphone, the phonocardiograph the tuning fork the continuous tone series, and the noise apparatus are direct contributions of applied phonetics to clinical diagnosis It is astonishing, too how various the applications of electrical science to diagnostic technic have been In recent years, these have grown very rapidly The testing of the functions of muscles and nerves by the faradic current and by the galvanic current were early methods of employing electrical science in the service of medical diagnosis The uses of electricity for the illumination when instruments of inspection are employed on clinical examination, have been more recently recognized and these modes of applying electricity in medical practice have become ever more important and helpful to the diagnostician and therapeutist Furthermore, the applications of electricity in roentgenological work are now manifold and by no means simple, as every expert X ray worker sooner or later learns A general knowledge of heat light sound electricity, and magnetism is, therefore, obviously essential for good work in medical diagnosis

One of the most important influences of the study of physics on the science of diagnosis is the understanding that the former subject gives of the different forms of energy and of the law of conservation of energy during transformation as they concern the human body When we recall that stimuli are in the last analysis physical agencies namely forms of energy that excite or depress the several functions of the living body we realize how important a role applied physics must ultimately play in physiology and accordingly in diagnosis The studies of direc

the stimulation in lower forms of life (phototaxis chemotaxis thermotaxis galvanotaxis etc) show us clearly certain of the directions that research must take if we are later on to understand more clearly than we do now the activities of the cellular constituents of the human body in health and in disease

As diagnostic work grows gradually more precise it makes ever greater use of certain standards of measurement that we owe to the physicists. Quantitative work in physics has been greatly facilitated by the selection for each measurable magnitude of a physical unit or standard of reference, with the aid of these units other similar quantities can by comparison be numerically defined Fortunately, since physicists have become convinced that one form of physical energy is convertible into another and that the change takes place according to definite laws, it has been possible to coordinate these several physical units The most fundamental units are those of length mass and time—the centimeter the gram and the second (hence the name CGS system of units) All other physical units of measurement take account of these fundamental notions of length mass and time In mechanics the unit of force is the dyne the unit of work is the erg the unit of power is the watt the unit of energy is the joule In the physics of heat the unit of heat is the calorie In electricity the unit of resistance is the ohm the unit of current is the ampere the unit of electromotive force the volt etc. These units are coming ever more into use in clinical diagnostic work Their general adoption in scientific work is a forcible example of the fundamental relation in which physics stands to all the more complex sciences of nature

The physical sciences then including as they do dynamics mechanics the physics of heat light sound electricity and magnetism energetics and the setting up of units to be used as standards of measurement are seen to be essential as a part of the basis upon which a science of diagnosis can be built Medical educators have been wise therefore in making knowledge of the theory and some skill in the use of the practical technical methods of physics a prerequisite to the study of medicine and of diagnosis

Relations of Diagnosis and Chemistry

The science of *chemistry* stands in almost as fundamental a relationship to the science of diagnosis as does the science of physics Chemistry has to do with the study of the composition of substances and of the changes in composition that substances undergo whereas physics which we have just considered studies rather the properties of substances In physical chemistry in process of development we see a new

science that attempts to correlate the physical properties of substances with their chemical composition Our knowledge of the composition of the substances in the cells and in the fluids of the human body has already become very important for the student of the science of diagnosis Indeed it could scarcely be otherwise since the fact of the life of the human body is metabolism The living substance is on the one hand ever undergoing decomposition (dissimilation or catabolism), and on the other is ever undergoing reconstruction (assimilation or anabolism) With the exact composition of the most complex types of chemical substances existing in the body—the hypothetical biogens—we are as yet unfamiliar, but of the importance in their composition of the long chains of amino acids known as proteins we have now become convinced Physiologists and physiological chemists have already gone far toward demonstrating to us how the foods taken into the body are changed in order that suitable building stones may be available for the construction of the complex biogen molecules of protoplasm and they are also revealing to us the various stages in the degradation processes through which these biogens form secretions and excretions as end products of the body metabolism The fascinating studies that deal with the morphological changes with the chemical changes, and with the energy changes that accompany the body metabolism were growing yearly more numerous before the outbreak of the great war, they will doubtless be resumed with even greater vigor now that the war is over and the nations can again settle down to the leisurely and undisturbed cultivation of medical science The principles and the practical technical methods of chemistry are now a part of the stock in trade of the well equipped student of diagnosis

If then the modern diagnostician needs to be tolerably familiar with the principles and the methods of chemical science his preparatory studies should include inorganic chemistry, organic chemistry, analytical chemistry and physical chemistry The medical diagnosis of to-day makes extensive use of the principles of the terminology, and of the machinery of all these subdivisions of chemistry The work of diagnosis in the clinical laboratory demands considerable practical acquaintance with the apparatus and the technique of chemical manipulations In the clinical investigation of metabolism especially a knowledge of chemistry and an acquaintance with chemical methods is essential. I need refer only to the chemistry of the proteins and of their derivatives and its applications to metabolism in the renal diseases and in the amino-acid diatheses to the chemistry of the carbohydrates and its applications to metabolism in diabetes mellitus and allied disturbances, to the chemistry of the fats and its relations to obesity on the one hand and

to acidosis on the other to the chemistry of the mineral substances in the body and its relations to the metabolism in rickets in osteomalacia and in tetany, to the chemistry of the nucleins purins and pyrimidins and its relations to the metabolism in gout and finally to the as yet little known chemistry of the vitamins and its relations to the metabolism in beri beri and in other diseases in which there is believed to be vitamin deficiency If I were to day a student in my teens looking forward to the study of diagnosis and therapy and could realize at that age as I do now the fundamental importance of physical and chemical science for the future of the biological and medical sciences I should make a great effort to become firmly grounded in the different branches of physics and chemistry securing also sufficient training in mathematics to permit of their higher study Young students of to day who will avail themselves of this hint before going on to the study of the bio logical and medical sciences will I feel sure be richly rewarded when they become the diagnosticians and therapeutists of twenty years from now The time and energy expended in the acquisition of sound and thorough physical and chemical experience as a preliminary to medical study could scarcely be better employed

Relations of Diagnosis and Biology

The relationship of the science of diagnosis to the science of *biology* is obvious and yet there should be no confusion or overlapping as regards their respective fields As abstract sciences biology deals with the laws of life diagnosis with the laws of the recognition of health and of disease in living organisms Each science is important for the other though each differs from the other From biology we learn that the tendency of evolution is to transfer the maximum amount of inorganic matter to the organized state as a part of the general process of storing cosmical energy The most complex chemical combination known is protoplasm the ' physical basis of life In biotic organization the unit is the cell a very complex structure when compared with the relatively simple constitution of protoplasm Biology treats of unicellular and multicellular organisms of their structures and functions of their origin growth and destiny It reveals the advantages of living beings as organized mechanisms for the storage and expenditure of energy It studies reactions between organisms and their environment and shows how capacity for suitable adjustment makes for success and survival and how inability adequately to adjust leads to failure and extinction It explains the origin of anatomical structures and the relations of structures to functions It discovers that at certain stages of biotic organization feeling becomes important for the preservation of life that

pleasure and pain are conditional to the existence of plastic organisms and that out of sentiency, mind develops Knowing, feeling, and striving become ever more important factors in the living of higher organisms Some kinds of structure, some varieties of function, and some modes of feeling, striving, and knowing are advantageous to organisms and make for their survival, others are disadvantageous and lead to disease or death of individuals and of species Evolution heredity, variation adaptation, and selection, as studied by the biologist are all important as building stones in the foundation of a science of diagnosis

The relation of diagnosis to one of the special biological sciences *anthropology*, may be considered from two points of view The student of diagnosis looks upon the science of anthropology as a part of the foundation for the science of diagnosis, whereas the anthropologist will look upon that part of diagnosis that deals with the recognition of health and of disease in man as belonging to the science of man Undoubtedly the two sciences overlap and the facts and phenomena of each are important for the other science Anthropology as a descriptive science is really a branch of zoology A knowledge of the peculiarly human characteristics which anthropology supplies is too often disregarded by students of the science of diagnosis who transfer without criticism conclusions drawn from observations upon experimental animals directly to the human sphere Of the different departments of anthropology, it is somatology (dealing with man s physical constitution) and technology (dealing with man s products material and institutional) that are most important for the student of diagnosis Among the institutions man has produced are languages customs governments, religions industries art and literature How inadequate would be the work of the student of diagnosis who lacked familiarity with these achievements of man! Both the natural history of man' and the "history of culture" supply data that are essential for the construction of a science of diagnosis

The biological sciences deal then with living organisms and patients who consult physicians are living organisms that conform to biological laws All the special biological sciences including (1) Morphology which deals with the statical aspects of the organic world or with the structure of living organisms (2) Physiology which deals with the dynamical aspects of the same world or with the properties processes and functions of living organisms (3) Distribution which deals with the number of organisms of different kinds in different parts of the world and (4) Evolution or Etiology which deals with the natural history of the cosmos in as far as it concerns organic beings can contribute to the science of diagnosis That training in the principles

and methods of the biological sciences should like similar training in the sciences of physics and chemistry be now regarded as an essential prerequisite to the study of medicine and diagnosis seems therefore a reasonable opinion for the medical educator to hold

Relations of Diagnosis and Psychology

Turning to another subject, it is surprising how little attention has been paid by those who frame pre medical curricula to the importance of the relations of the science of *psychology* to the science of diagnosis

Psychology, as the science of mind, embraces not only the phenomena of intellect but also those of the affections and those of the will Students of human psychology study the knowing the feeling and the striving of man Biology has shown us that feelings of pleasure induce lower animals to look for food and to eat it and to perform the acts that reproduce their kind whereas feelings of pain lead them to make efforts to escape from enemies and from other dangers Among higher animals the knowing element became ever more helpful to the feeling and the striving elements of mind in attaining the purposes of the organism Man is the most highly favored of all living creatures in this respect and by virtue of his intellect has not only obtained dominion over other forms of life but has also become the conqueror of the physical forces of nature Feeling is dynamic intellect is directive the will is an activity of purposive behavior that is determined by feeling and intellect

In the animal series the intellect seems to have developed at first as a means of increasing agreeable feeling of overcoming obstacles to the satisfaction of desires The knowing element gradually became a most important servant of the feeling' and striving' elements of the mind The human pleasures include the realization of certain objective ends—the nutritive the reproductive the esthetic the emotional the moral and the intellectual The desire for self realization and to obtain pleasure (lower or higher') is the motive to effort. The intellect is to be looked upon as a directive agent to guide the organism in the achievement of its purposes that is in the satisfaction of its desires and in the fulfilling of all its capacities It manifests itself in foresight cunning shrewdness sagacity wisdom tact ingenuity inventiveness art science and philosophy

The psychologist observes and studies his own consciousness and the behavior of men and of animals and builds up his science upon the basis of the facts thus accumulated He desires to understand and to explain his own behavior and that of other men and of animals Knowledge of consciousness and of behavior will he believes yield the power

to guide and control behavior He defines behavior as the manner in which an organism possessing mind conducts itself in the active pursuit of its own welfare and in the effort to reach its own ends or to effect its own purposes By studying himself and observing the phenomena of his own consciousness and his own behavior (as he, himself, thinks and feels and strives), he deepens his understanding of the behavior of all living things and draws conclusions regarding the consciousness he believes they must possess when they exhibit behavior By systematic studies of this sort the laws of mind are established

In analyzing and describing the stream of his own consciousness the psychologist meets with very great difficulties and the overcoming of these constitutes an important part of his problem He designates the knowing aspect of mind as "cognitive," the feeling aspect as "affective," and the striving as "conative" He seeks to explain both what goes on in consciousness (and the accompanying behavior) on the basis of the "constitution" or the "structure" of the mind, as it develops during the life of the organism, a development that is determined partly by heredity and partly by environmental influences that favor or prevent the realization of the various hereditary possibilities He conceives of the mind as constituted of a large number of 'mental dispositions' which form organized systems The totality of cognitive dispositions he speaks of as the "knowledge" possessed by the mind, the totality of affective and conative dispositions he refers to as the "character" of the individual Acquaintance with the knowledge and character of a person gives the clue to his conduct in a given situation Despite the difficulties of analysis and description psychologists are gradually arriving at conceptions that are helpful both for theory and practice

Now the science of diagnosis is very largely dependent upon observation of the behavior of patients and necessitates inquiry into their mental states in their cognitive, affective, and conative aspects Most physicians whether or not they have had any academic training in psychology acquire a certain power of estimating intellectual capacity and of recognizing types of character For the higher reaches of diagnosis however, a much fuller acquaintance with the laws of mind and the phenomena of human behavior than can be obtained without special training in psychology is requisite Diagnostic science and the art of diagnosis are now being rapidly promoted by men who have been thoroughly trained in psychology as a whole or in one or more of its branches A larger acquaintance with the psychology of the normal human adult with the psychology of animals with the psychology of children, with the individual psychology that deals with the peculiarities

of individual minds with abnormal psychology and with the social psychology that studies the folk mind the crowd mind, and the group-mind, and their influences upon individual minds through the processes of suggestion sympathy imitation and interpenetration will doubtless before long, be regarded as an essential part of the equipment of the earnest student of diagnosis

Relations of Diagnosis and Sociology

We come next to the kinship of diagnosis and sociology It is not easy sharply to separate sociology from psychology social psychology is a link that joins these two sciences In studying psychology nowadays the prospective student of diagnosis learns as has just been said of the importance of the crowd mind or ' mass mind exhibited by large masses and of the group-mind that is manifested by smaller associations in every highly organized human society He studies the principles of collective thinking collective feeling and collective acting and he makes an effort to observe the influence of the social *milieu* upon the development of the individual mind But the science of *sociology* itself is also closely related to the science of diagnosis and a fairly comprehensive grasp of its methods and principles should be acquired by those who expect to study and to practice diagnosis Diagnosis has to deal with the recognition of disease' in individuals but these individuals are members of social groups To understand an individual thoroughly one must know much about the social groups to which he belongs and their origin by ascent or descent A knowledge of sociology should therefore be helpful to the student and practitioner of diagnosis

Sociology the science of society, studies the structure functions and genesis of the social body, just as anatomy physiology embryology and psychology study the individual organism It discovers what it is in man s nature that induces him to associate himself with others what the effects of association are upon his interests his feelings his emotions his desires and his acts what purposes association and cooperation subserve and what means are adopted for favoring them what relations become established among men as a result of different kinds of aggregation and cooperation and what influence these relations exert upon the thought the feelings and the behavior of man Sociologists like J S Mill A Comte and Lester Ward have traced the broad outlines of the science and a host of workers are filling in the details The data of sociology are drawn from a large number of special social sciences (ethnography ethnology technology archeology demography history economics jurisprudence politics and ethics) these data form the basis of the reasoning and the generalizations of the more general

science The forces studied by the sociologist are psychic, they consist of human motives, the unsatisfied appetites and desires of men These forces are preservative, reproductive, esthetic, moral, and intellectual—in other words, the "forces of individual preservation" the 'forces of race continuance," and the "forces of race elevation" Feeling is the dynamic agent in society and intellect is the directing agent Resulting from the collision of social forces, states of approximate equilibrium occur among them and social structures (including the family the clan the tribe the state, the church, and other voluntary associations) and social institutions (including marriage, customs, language, codes, religions arts literatures and sciences) arise These structures and institutions, while relatively stable, are constantly undergoing change, though there is at every time a social order, there is at all times some social progress, and this progress is described by the sociologist as partly the result of an unconscious evolution (social genesis) partly the result (and increasingly so now) of the conscious application of the intellect as a guide to human desires in avoiding obstacles to their satisfaction (individual and collective telesis) Knowledge of these social structures and functions and of their evolution therefore, constitutes the science of sociology None of the better diagnosticians of our time is likely to underestimate the importance for his own science of a knowledge of society, of social structures of social institutions or of social functions For the physician is constantly called upon nowadays, to recognize in his patients states in which there is maladjustment of the individual to his environment states in which the reciprocal relations of the individual and of the social groups to which he belongs are unsatisfactory, states that cannot be properly understood or adequately modified by a therapeutic regimen when the individual is studied alone without concomitant consideration of the group or groups, of socii to which he belongs The prospective diagnostician should, therefore receive sufficient training in the science of sociology and should familiarize himself with the laws of association and with the subtle psychic processes of interpenetration that characterize the activities of concrete groups

Relations of Diagnosis to the Preclinical Medical Sciences

Though some acquaintance with the sciences of physics chemistry biology anthropology, psychology and sociology including ethics and politics is as has been emphasized above highly desirable as preparatory experience for the student of the science and for the practitioner of the art of diagnosis a still more comprehensive training is necessary in certain distinctively medical sciences namely in a group of sciences intermediate between the fundamental sciences above referred to and

the clinical sciences of diagnosis and therapy This intermediate group of sciences training in which is indispensable for the prospective clinician is usually taught in the first two years of the course in the medical school, these sciences we may include under the general name of *preclinical medical sciences* This group includes several sub groups (1) an anatomical sub group (gross human anatomy micro scopic anatomy histology, cytology, and embryology), (2) a physio logical sub group (general and special physiology physiological chem istry and pharmacology) and (3) a pathological sub group (general pathology special pathological anatomy and histology bacteriology parasitology, immunology, psychopathology and social pathology) These preclinical sciences were largely developed in the first place by diagnosticians (as postclinical sciences) because their development was necessary for the growth of diagnosis and therapy but as knowledge has grown and technique has become ever more complex they have come to be cultivated as sciences for their own sake by men who devote their whole time and energies to the single provinces and they are now taught and should be taught (as far as developed) as prerequisite to work in diagnosis The facts and principles of these preclinical sciences supply data that are necessary as a basis for the science of diagnosis It is essential that the scientific diagnostician shall himself have had a general training in the methods and principles of each of these pre clinical medical sciences and that he shall have acquired such a com prehensive grasp of them as will permit him first to keep pace with their progress during his lifetime and secondly to make applications of them in any direction that will be helpful to his own science and art

It must be emphasized however that the problems of the pre clinical medical sciences though closely related to the problems of the science of diagnosis are by no means identical with them There is much overlapping but it is desirable that the purposes of each of the sciences should be kept clearly in view by those who represent it The anatomist should work at the problems of his science for their own sake for the sake of discovering facts and truths regarding the form and genesis of the structures in organisms and especially in the human organism without special reference to their applicability in the science of diagnosis It is the business of the investigator in the science of diagnosis to make the application of the facts and truths of the ana tomical sciences and their methods to the solution of diagnostic problems The same is true as regards the physiological sub group of the pre clinical medical sciences It holds even for the pathological sub group which many would look upon as an integral part of the science of diagnosis but the aims purposes and methods of the representatives

of the special sciences of pathological anatomy, pathological physiology and bacteriology are and should be somewhat different from the aims purposes and methods of the representatives of clinical diagnosis Closely related as the clinical and preclinical medical sciences are they are still separate and distinct, and much is gained for both groups by the maintenance of this separation and distinction

Each science will help its kindred sciences most by defining strictly the limits of its province and cultivating industriously, intensively, and conscientiously its own fields within that province The clinician must not expect the anatomist, the physiologist, and the pathologist to leave their own special tasks to solve his diagnostic problems for him, nor should the worker in clinical diagnosis be expected by his preclinical colleagues to neglect the crops on his own acreage by yielding to the temptation to till promising neighboring fields When special needs are felt and lead to a division of work, dormant capacities are aroused and new powers are called into being The differentiation of purposes and of labor is one of the most powerful influences for increasing the range of intellectual activities and for stimulating their development

In diagnosis itself, the field is so large that no single person can expect to work equally well in all parts of it A division of labor in diagnosis partly methodological and partly regional and systematic, has proved profitable as in science at large As evidences of this division *we find diagnostic workers distributing themselves more or less* (1) according to the methods they employ (applied physics, applied chemistry applied biology applied psychology, applied sociology, applied physiology applied pathology, etc) and (2) according to the systems and regions they especially study (angiology, neurology, psychiatry, gastroenterology, dermatology laryngology, ophthalmology orthopedics gynecology, etc) Diagnosis by cooperative groups with an integrator who after collection of data and consultations with collaborators, synthesizes the total findings of the group and composes the clinical picture with balanced ordination of its parts, is the highest expression by the diagnostic art of to day of the unity obtainable despite this differentiation, and of the profit derivable from specialization

The Pure Science of Clinical Diagnosis

Though the pure science, the applied science and the art of diagnosis are most often treated together it is helpful for purposes of analysis to make the division and to understand how the three differ one from another

By the *pure science of diagnosis* we mean the part of the subject that deals with the general laws and principles of diagnosis that is,

with the laws and principles that govern the recognition of health and of disease The laws of diagnosis are generalizations that epitomize in brief formulae uniformities of coexistence and of sequence among the phenomena of health and of disease The causes of these uniformities are natural forces operating under like conditions The forces concerned are physical chemical biotic psychic and social, and the pure science of diagnosis is gradually moving toward the recognition of the workings of these forces as manifested in the phenomena of health and of disease In the construction of this pure science of diagnosis the data are derived from all the sciences already referred to as fundamental for diagnosis as well as from all the special diagnostic sciences The storehouse of knowledge and of truths discovered in the science of diagnosis is already a very large one Facts have been classified and are ever being more successfully reclassified as the laws underlying them and the causes of the uniformities are being ever better recognized Subjective symptoms and physical signs are grouped together as symptom complexes (or syndromes) and these are uniformities of coexistence and of sequence that betoken underlying causes acting under like conditions, and these causes and these conditions are slowly being determined by the host of investigators who are ever eagerly striving to discover them Through observation experimentation and reflective thinking knowledge concerning the symptoms of disease disease complexes the sites of disease the structural and functional alterations in disease and their genesis the forces concerned and the conditions under which they act is being organized as a science of diagnosis with some well established principles The diagnosis of disease now includes (1) a recognition of disturbed function in disease (pathological physiological diagnosis) (2) a recognition of the site and nature of the structural changes in disease (pathological anatomical diagnosis) (3) a recognition of the causes of disease (etiological diagnosis) and (4) a recognition of the relation of causes to the sequence of conditions in the disease (pathogenetic diagnosis) The data accumulated by workers in all the medical sciences are gradually being summarized arranged and classified by workers in the science of diagnosis so that the laws and principles underlying them are slowly becoming evident

The Applied Science of Diagnosis

Pure science applied science and art progress contemporaneously Each plays into the hands of the other two there are ever reciprocal contributions to healthy growth

The applied science of diagnosis has the task of finding out how the laws and principles of the pure science of diagnosis can best be

applied in the practical work of recognizing health or disease in persons who present themselves for examination This applied science of diagnosis perceives the utilities of the truths of "pure" science and sets about devising the means of adjustment that are necessary to actualize them It invents methods tools contrivances and systems of procedure in other words, the "machinery of diagnosis" It calls to the service of diagnosis, from the other sciences, any fact, truth, principle, or invention that it can make use of directly or indirectly, as an aid It becomes familiar with the methods and instruments of mathematics, chemistry biology, psychology, physics, anatomy, physiology, pathology bacteriology and immunology, modifying them where necessary to meet its own needs It extends the simpler methods of observation of patients by utilizing instruments of precision or special methods that enormously multiply and refine the possibilities of sense impressions Thus the sense of sight is extended by photography, and by the use of the microscope, the spectroscope, the ophthalmoscope, the bronchoscope, the cystoscope the roentgenoscope and a hundred other devices The senses of smell and of taste are chemical senses that unaided carry us only a short way in collecting chemical data as compared with the fact accumulation regarding chemical conditions in the blood secretions excretions and effusions made possible by the clinical chemists adaptations of methods devised by workers in physiological and pathological chemistry The sense of hearing is extended by the stethoscope the microphone and the phono cardiograph The temperature sense is supplemented by the clinical thermometer The sense of touch and pressure is subtly refined or replaced, by various ingenious devices such as the sphygmograph the tonometer the balance the dynamometer and the string galvanometer The time honored methods of inspection palpation percussion auscultation and mensuration have gradually become expanded into an observational and experimental technique that is subtle and complex but which makes for ever greater objectivity and precision Thus by devising practical technical methods that can be easily made use of in examining patients, the applied science of diagnosis is ever better able to turn to account the truths and principles that students of the pure science of diagnosis have established

Workers in the applied science of diagnosis are also making many efforts better to organize the mode of conducting clinical examinations and more logically to arrange the several steps that necessarily must be taken to arrive at satisfactory diagnostic conclusions That the procedure of collecting the data upon which a diagnosis is based and of making clinical records of the course of disease processes has been systematized in the interests of thoroughness completeness and accu

racy, can easily be seen by comparing the contents of the clinical histories kept to day (anamnesis status praesens catamnesis epicrisis) with those that have come down to us from the diagnosticians of earlier generations Moreover, the methods of applying reflective thought to the consideration of the phenomena observed for the purpose of recognizing syndromes lesions causes and prospects are being brought into accord with the general method of science and with the newer logic The purpose of a diagnostic study decides what methods shall be applied and how In every case there must first be a recognition of the existence of a diagnostic problem observations and experiments are then made to locate and more accurately to define that problem the phenomena observed are arranged and brooded over until suggestions of possible explanation or recognition of meaning occur to the mind the implications of each interpretative suggestion are reasoned out a comparison is made between each suggestion with all its implications and the facts as already collected or as extended by further observation and experiment and finally *a decision is reached that there is sufficient reason* for the acceptance of one or another of the diagnostic inferences through corroboration and for the rejection of other suggestions that are proved invalid through failure of corroboration If no suggestion that has been entertained can be found to be valid no diagnosis is made the mind is still kept open and judgment is kept suspended until the process has been gone through with again An attempt to accumulate more facts has then to be made the occurrence of further diagnostic suggestions is thus favored and these in turn are reasoned out as to their bearings and tested for their validity In this way the best diagnoses of which the examiner is capable in the existing state of his knowledge ability and opportunities are reached The representatives of the applied science of diagnosis through devising new and better methods of *examination through arranging for their more orderly em*ployment and through conforming to the usages of a sound logic occupy therefore an important position mediating between that of the pure science of diagnosis and that of the diagnostic art

The Art of Clinical Diagnosis

By the exercise of *the art of diagnosis* is meant the skillful carrying out of the plans and methods of the applied science of diagnosis (based upon the laws and principles of the pure science) in solving actual problems of recognizing health and disease in persons who present themselves for examination

Expertness in performance and capacity to make and deliver a valuable product characterize the diagnostic artist whether he is active

in special domains only or whether he attempts to make a more general diagnostic survey Many physicians have acquired an extensive knowledge of the classifications of disease, of pathological anatomy and physiology, and of etiology have become familiar with descriptions of the practical technical methods in use, and have observed skillful practitioners of the art of diagnosis at work but have never arrived at expertness and facility, themselves, in the actual performance of diagnostic tasks There are other physicians who though they may have attained to real skill in the execution of certain diagnostic procedures, have never become good general diagnosticians owing to lack of a comprehensive grasp of the fundamental laws and principles of diagnosis or owing to insufficient acquaintance with the practical-technical methods of diagnostic work other than a few in which they have acquired accuracy and facility Mere exactness in outlining an area of dulness by percussion mere faultless objectivity in description of the sounds audible over the heart and lungs, or mere precision in the conduct of a roentgenoscopic examination of the cardiovascular stripe, in the recording of a sphygmogram, or in the quantitative estimation of blood sugar, valuable though any or all of these procedures may be in collecting data to be used in the reasoning process that precedes the arrival at a legitimate diagnostic conclusion, can be exhibited by men who dare lay no claim to mastery of the general art of diagnosis As a matter of fact, a laboratory *Diener* may learn to carry out the technique of the Wassermann reaction or of the differential count of the white corpuscles of the blood, just as accurately, and perhaps more speedily, than the physician who employs him and who has instructed him but no one would think of regarding such a laboratory helper as proficient in the general art of medical diagnosis Owing to the lower dignity of his employment, he must be regarded as an artisan rather than as an artist An adept in an art of medical diagnosis that is not merely local or special in its aims must have acquired at least some skill in the collection of data in all the domains pertinent to general medical diagnosis and must possess that wide understanding of the truths and principles of diagnostic science and that ability in applying them that will permit him on reflective thinking about the phenomena observed by himself or by those who are associated with him to arrive at a diagnostic conclusion or belief that is warranted Ability to do diagnostic work quickly accurately and effectively and capacity to produce diagnostic results that are adequate to the purpose in view are then the marks of an operator who is skilled in the art of diagnosis

The attainment of real skill in the general diagnostic art is no easy matter It presupposes in addition to good natural endowment a thor

ough general and special education for the developing artist At the basis of our present-day conception of the training of medical students lies the recognition of (1) the desirability of a collegiate education pre *liminary to the study of medicine* (2) the need of a thorough instruc tion in the preclinical sciences and in the organized body of knowledge that we call the pure science of medical diagnosis and (3) of the importance of a closely supervised systematic education in the practical technical methods of accumulating facts pertinent to diagnosis and in the logical way of making use of these facts (by grouping them by drawing inferences from them by testing these inferences carefully for their validity and by finally reaching legitimate diagnostic conclusions) The requirements for admission to the better medical schools of our time are such that the students entering the schools have had ample opportunities for becoming habituated to the method of science and for acquiring a good general knowledge of nature and of man as an individual and as a member of social groups The students have all had instruction in mathematics physics chemistry and biology and many of them have studied also psychology logic and sociology In addition to a training in the use of their native language they have acquired a reading knowledge of one or more modern foreign languages have learned the technique of using libraries and have discovered the value of consulting sources through bibliographies The prospective medical students with such a preliminary training can scarcely have avoided becoming acquainted with the general methods and tools of scientific inquiry They have learned how problems are set and solved They have been taught the necessity of taking pains in collecting facts by the accurate and detailed observation of phenomena and have come to appreciate the special value of experimentation in which observations are made under rigidly controlled conditions Under the guidance of good teachers they have begun to acquire the habit of reflective thinking in dealing with their perplexities They have become unwilling to jump to conclusions and have learned to insist when confronted with a dif ficulty on *temporarily suspending judgment* and on collecting informa tion that will more rigidly define and locate that difficulty and when suggestions of possible solution of a problem have occurred to them on brooding over their facts they have been taught to reason out the bearings of these suggestions to compare them and their full implica tions with the actual facts before them and thus to test the tentative ideas of solution for their validity they have learned the importance when necessary of making more observations and experiments that will either corroborate or refute In other words they have had the opportunity to practice deliberative thinking before undertaking their

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arrive finally at diagnostic ideas that can be corroborated Though the students are encouraged to work independently as far as possible they have also the great advantage that the facts they collect and their reasoning about the facts are subjected to frequent review and criticism by the resident hospital assistants and by the older and more experienced visiting physicians Only after this long training in college medical school and hospital is the student fitted to undertake the perfecting of his skill in the art of diagnosis and long experience in practice may still be required to make him truly expert

The Actual Process of Clinical Diagnosis

If diagnostic results commensurate with the medical knowledge of the time are to be reached when an internist is asked by a patient to make a diagnostic study, the procedure that he must adopt will be somewhat prolonged and complex and may be divided into several different stages (1) the recognition of a problem to be solved and the feeling of a diagnostic difficulty, (2) the accumulation of data that help to locate and to define the diagnostic problem (3) the consideration of the data (accumulated summarized and arranged) that suggestions of possible solution of the diagnostic problem may occur to the mind (4) the elaboration by reasoning of the detailed bearings of the several suggestions of solution and (5) the careful testing of the suggestions thus minutely worked out as to their bearings by comparison with the facts accumulated supplemented when necessary by other facts obtained by further observations and experiments this careful testing leading to disbelief in the unverifiable suggestions and finally to belief in the suggestions that are found to be valid in other words the arrival at diagnostic conclusions Each of these five stages is a necessary part of any diagnostic study that aims at accuracy and completeness

The course pursued by a worker in clinical diagnosis then is similar to that followed by everyone who engages in reflective or deliberative thinking in order to solve his problems Thus the same five stages must be passed through by a business man of the higher type when he is confronted by a new and problematic industrial adventure The same stopping places occur in the path of an engineer who is given the task of constructing a bridge And the same points are recognizable in the line along which any scientific investigator moves when he scents a problem that interests him goes energetically to work to solve it and finally meets with success There is only one satisfactory method for solving problems no matter what the domain and that method is the method of deliberative thinking commonly known as the "method of science

medical studies proper On entering the medical school they spend a couple of years in work in the simpler preclinical medical sciences before engaging in the much more complex work of the clinical sciences of diagnosis and therapy In the laboratories of anatomy, of physiology, of physiological chemistry of pharmacology of pathology and of bacteriology they continue their training in the applications of the method of science to the study of the phenomena dealt with by these special sciences and they should come out of these laboratories with that background of knowledge and that familiarity with methods that is indispensable for any proper study of the science and any skillful practice of the art, of medical diagnosis In the clinical departments of the medical school the students then enter courses of instruction in the laws and principles of diagnosis and therapy, begin their education in the technical methods of these sciences and, under the closest supervision make a start in the practice of the corresponding arts Not only must the methods be learned (the applied sciences of diagnosis and therapy), but skill in carrying them out (the arts of diagnosis and therapy) must be acquired in order that the students may acquire confidence in the reports that their sense-organs (thus refined) yield and in the warranty for the diagnostic conclusions that can be reached and the therapeutic regimens that can legitimately be outlined by the application of reflective thought to these reports This training in the clinical departments includes instruction in history-taking, in general physical diagnosis, in clinical laboratory work, in X ray work, and in the technique of a whole series of special and instrumental methods of examination The students learn the clinical application of bacteriological and immunological methods to be used in the diagnosis of the infectious diseases, they are taught how to examine the respiratory apparatus the circulatory apparatus the blood the digestive system the urogenital system, the locomotor system and the nervous system and its functions, and they also receive instruction in the methods of clinically investigating the processes of metabolism and the functions of the endocrine apparatus After this more or less thorough drill in the use of the methods of collecting facts regarding each special domain they begin as clinical clerks working in hospital wards and dispensaries to take up the complete diagnostic study of single unknown cases In close association with, and under the strict control of, experienced diagnosticians they record anamneses make physical and psychical examinations resort to laboratory tests and X ray tests are present at and observe closely the examinations made by experts in special domains, summarize and rearrange the total findings entertain tentative ideas of diagnosis based upon these consider all the implications of such suggestions and try to

make an effort to discover the cause of the headache in the hope that we may be able to apply a rational treatment we are not content with any single prescription to be used in all cases of headache Similarly if a man complain of a backache the scientific practitioner of to-day will not resort at once to manipulative or other therapy, but will first undertake a thorough investigation of the case he will try to understand the pathogenesis of the condition before he decides upon the form of treatment to be applied Thus a realization of the difficulties of diagnosis protects one from the extreme naivety in therapy that formerly prevailed

Even those who have been educated in the best medical schools sometimes fail to apprehend clearly the extent of the diagnostic study that is necessary in certain cases to insure the patient that he shall receive the full benefit derivable from the diagnostic and therapeutic methods that are available A practitioner may be tempted at times to make a 'snap shot diagnosis and to be content with it but if he yield to this temptation often and curtail his diagnostic studies correspondingly he will have occasion sooner or later to rue some of his hasty conclusions The larger the experience one has had in diagnosis the more often has he demonstrated that clinical conditions that at first seem exceedingly simple may turn out to be very complex In many cases it is only after numerous data have been collected that the real nature of the physician s problem becomes apparent In order then that the diagnostic study of a given patient shall be sufficiently comprehensive the physician must have an adequate appreciation of the diagnostic difficulty that confronts him

One of the principal causes of detrimental curtailment of diagnostic study probably lies in feeble curiosity The instinct of curiosity is of course a part of our common endowment When we see or hear something that we do not fully understand this instinct should come into function We should have a feeling of wonder and we should be driven by an impulse to approach and examine carefully the object that excites our wonder Different persons are doubtless endowed in variable degree with this inborn impulse closely to examine objects that excite their wonder The impulse grows stronger through exercise weaker through neglect. It is probable that many persons endowed with an instinct of curiosity of normal strength fail to profit by it as they should owing to faulty education A normal child exhibits regularly the workings of the instinct and the medical student and the physician should to a certain extent try to remain childlike in this respect In clinical diagnosis especially the mind should be kept ever on the alert ever sensitive to anything out of the ordinary ever eager for new experi

Nowadays a modest internist makes no claim to powers of diagnosis *von Gottes Gnaden* instead, he recognizes the necessity of subjecting himself gracefully to the laws of logic that must be obeyed not only by him but also by his fellow-workers in the higher branches of human endeavor The clinician who sees and hears will often greatly wonder, he will then feed himself with questionings in order that reason may diminish his wonder He will observe and experiment, he will brood over and speculate upon his findings, his thick coming fancies will keep him from rest until he has tested them rigidly as to their validity in all their implications, he may even distrust his eyes and will wrangle with his reason until he has convinced himself that the evidence in favor of one set of conclusions, and of one only, is good and satisfying He will observe so accurately, he will experiment so appropriately he will imagine so vividly, and he will verify so conscientiously that his diagnostic conclusions will be readily defensible and will be concurred in by such other diagnosticians as are keen and honest observers skillful experimenters, and right reasoners Feeling a difficulty, observing and experimenting to define and localize it, harboring hypotheses that may solve it, reasoning about the implications of these hypotheses, and finally verifying those that are valid, are the successive steps in the stairway of the process of diagnosis Clinical diagnosis is, then, an arduous and composite process, its complexities and intricacies are unavoidable But practice in the use of the scientific method gives strength, speed, and insight to him who employs it Though the road followed by the reflective thinker may seem long steep and involved it is the only safe way to as much of certainty in diagnosis as the knowledge and technique of a given time will permit

Stage I The Recognition of a Problem to be Solved, Feeling a Diagnostic Difficulty

It seems worth while to make the feeling of a diagnostic difficulty a definite stage in the actual process of clinical diagnosis Formerly, more often than now a common cause of incomplete diagnostic study was a lack of realization of the difficulties that lie in the way of accurate diagnosis This was true especially in the times when dogmas prevailed among physicians In those times a single symptom say the complaint of the patient, often sufficed for the making of a diagnosis Thus a headache, a cough a palpitation or a pain in the epigastrium, gave rise to no diagnostic perplexity for the symptom itself was regarded as a diagnosis and the treatment could at once be undertaken for the universal principle or dogma left no doubt as to the course of action to be pursued If, nowadays a patient complain of a headache we at least

intelligent and experienced diagnostician should know not only when to deviate from a regular routine in a given case but also how to modify his routine from month to month and from year to year in order that his practice may keep pace with the advances of his science and his art The beginner in diagnosis does well nevertheless to adhere rather closely to a well thought-out scheme for the collection of data regarding patients, after he has attained to accuracy and celerity in applying this routine scheme, he may begin to consider the occasions when he is justified in modifying it or in diverging from it A systematic plan of collecting data is helpful both to the experienced and the inexperienced diagnostician

We may for convenience deal with the systematic accumulation of data regarding a patient in five different parts

1 The recording of the anamnesis

2 The recording of the results of a general physical and psychical examination

3 The recording of the results of the application of laboratory tests

4 The recording of the results of X ray examinations

5 The recording of the results of more intensive examinations of special domains

ad 1—*The Recording of the Anamnesis* In collecting the data obtainable as answers to questions put to the patient or to his friends one must make sure that the questionnaire covers (1) the main complaints of the patient (2) his family history (3) his personal history and (4) the history of the illness for which he consults the practitioner including the symptoms existing at the time It does not matter as a rule in what order these several parts of the history are taken Some physicians after ascertaining the main complaint of the patient prefer to begin with the family history to follow this with the personal history and to end up with a history of the present illness Others prefer to take the history of the present illness first and later to secure the family history and the personal history of the patient The latter method has some advantages for the patient is always more interested in talking about his present illness than in giving the details of the history of his family and of his earlier experiences Thus sick people often exhibit a certain impatience if one begin with the family history rather than with the history of the illness itself though after the latter has been given in detail they will willingly respond to inquiries regarding their family histories and their earlier personal histories In the accompanying table a general outline is given of the principal points to be covered by the ordinary anamnesis

ence The diagnostician should be always exploring continually seeking new materials for thought If he cultivate a healthy curiosity, if he foster the emotion of wonder, and if he keep strong the will to investigate in order that wonder may diminish, he will have provided the fundamental conditions that protect from one sided and incomplete diagnostic studies and that insure the comprehensive survey the accurate observation, the suitable experimentation and the careful reasoning that lead to valid diagnostic conclusions

Stage II The Accumulation of Data That Help to Localize and Define the Diagnostic Problem

Once having realized that we are confronted by a diagnostic difficulty, that we face a problematic situation, we enter upon the second stage of the diagnostic procedure and begin to accumulate the data that will permit us more accurately to define and to localize the diagnostic problem In other words we avoid any immediate attempt at solution of the problem because we desire first to get a better idea of the nature of the difficulty before us At this stage, therefore restraint of inference and suspension of judgment are desirable Even though suggestions of solution of the diagnostic problem arise in our minds as we proceed it is best not to yield assent to them at this stage even when they seem plausible, though it may be justifiable to pay as much attention to them as will help us to decide upon certain directions in which the investigation may be intensively undertaken or to conclude that in the particular instance certain tests often made in clinical studies may safely be omitted At this stage we must be sure that we drag our net over an area large enough to insure the enclosure of enough facts regarding the physical psychical and social status of our patient to make the diagnostic problem prec se in localization and definition

The accumulation of the data necessary for this purpose is greatly facilitated by the following of some systematic plan Thus it is customary to train medical students to collect the more important facts regarding a patient in a certain regular way The following of a routine method of procedure here has both advantages and disadvantages Among the advantages are (1) speed in the performance of an habitual process (2) comprehensiveness and (3) convenience of arrangement after the facts have been collected Among the disadvantages may be mentioned (1) the danger of stifling curiosity by too rigid adherence to a routine program and (2) the danger that routine may not be varied from time to time as knowledge grows as methods become elaborated and as changes of emphasis are seen to be important However the

often be a temptation to try to make short cuts and to limit the questionnaire unduly. Such abbreviation should be permitted only most cautiously, for even an experienced physician may easily overlook important clues if he deviate too far from his definite systematic plan of inquiry or if he reduce too much the number of inquiries he makes. A special warning to the beginner regarding interrogations concerning sexual, psychical and social details may be in place. It is often difficult to judge how far one ought to go in his inquiry at the first interview when such details seem to be of importance. The most sagacious and adroit inquirer will here sometimes make mistakes. It is therefore important for a beginner to go slowly and cautiously when he approaches this part of the anamnesis. He should try to elicit the facts in an easy conversational way, and he should especially avoid giving the impression that he is unnecessarily curious or offensively prying. It is only in certain cases that the details of the sexual life must be inquired into, and even then the mode and extent of the inquiry will necessarily be influenced by many circumstances, among which are the age, intelligence, character and experience of the patient. In determining the mental status of the applicant, too, good judgment must be used in deciding upon the nature and extent of the questions to be asked. One never asks a patient, for example, whether he has delusions! But if there be reason to suspect the existence of pathological ideas in the patient's mind, his answers to the four questions (1) Are you sick? (2) Have you been sad, blue, gloomy, depressed? (3) Do you blame yourself at all or anyone else for your trouble? and (4) Has everyone treated you well? will usually reveal the presence or absence of hypochondriacal, melancholic and paranoid ideas and will afford sufficient clues for the further prosecution or for the suspension of investigation in these directions. Psychoneurotic patients in whom it is often desirable to hunt carefully for so-called "psychogenic data" are often especially sensitive to inquiries regarding their personal lives and their adaptation to the social environment. If on cautious approach to this domain the patient be found unwilling to talk at the first interview, it may be wise to postpone this part of the inquiry for a time. A little later, after the confidence of the patient has been established by the thorough physical examination made and by the sympathetic attitude of the physician, it will be more easily possible to secure, should it be deemed important, the full avowal of the patient regarding his more intimate life. The reticence of patients regarding abnormal feelings and emotions, moods, ideas and experiences is easily understandable, and even though questions relating to these necessarily form a part of the daily work of the medical practitioner, it can scarcely be expected that all the patients will willingly

A Main complaints of the patient and their duration
B Family history (parents, brothers and sisters consort children other relatives)
C Personal history (habits of work eating drinking smoking exercising resting sleeping relaxing etc) education experience diseases operations, traumata mental conflicts social adaptations
D Present illness (onset supposed causes course previous treatment epitome of symptoms referable to different anatomical physiological domains)

It is important when recording the anamnesis to ask questions that bear upon the presence or absence of certain prominent symptoms referable to definite domains of the body, such inquiries are best made also in systematic sequence After one has formed the habit of such questioning a catalogue of the more important indications can be easily held in the mind But the beginner will do well while recording the anamnesis, to have before him a list of these symptoms to make sure that he overlook no inquiry that could be pertinent In this connection, the following list of betokening symptoms is a serviceable one

Prominent Symptoms

Pain (topography time relations severity quality radiations modifying influences associated phenomena)
Headaches
Dizziness
Tinnitus
Otorrhea
Nasal catarrh
Sore throat hoarseness
Cough sputum including hemoptysis
Dyspnea
Palpitation irregular action of heart
Retrosternal or precordial oppression or pain (relation to effort radiation)
Swelling of ankles or face varicose veins
Ingesta (quality quantity) Disturbances of appetite and of deglutition trouble with teeth and gums
Nausea vomiting including hematemesis
Gaseous eructations flatulence
Constipation diarrhea blood or mucus in stools hemorrhoids fistulae.
Herniae
Pollakiuria dysuria polyuria nocturia hematuria pyuria
Disturbance of sexual functions (male female)
Symptoms referable to muscles bones or joints including the spine
Skin eruptions pigmentations pruritus loss of hair or nails
Disturbances of motility (paralysis weakness wasting rigidity twitching tremor spasms cramps fits ataxias *dysarthria aphonia* aphasia apraxia)
Disturbances of sensibility (anesthesia hyperesthesia paresthesia especially tingling in the fingers and toes defects of smell taste sight and hearing)
Mental disturbances (nervousness insomnia amnesia fainting spells or other losses of consciousness delusions [hypochondriacal melancholic or paranoid] exaltation depression loss of interests fears indecision inability to concentrate feelings of unreality social maladjustments)
Obesity emaciation changes in weight
Signs of infection (fever chills sweats petechiae etc)

The experience and common sense of the examiner must guide him in the application of his questionnaire in any given case There may

of the pathological phenomena self observed by the patient will be omitted from the record and the examiner can be confident that he has at hand the data necessary for his guidance in the further progress of the diagnostic investigation, these particulars are helpful for the making of decisions regarding the necessity of more intensive explorations in certain domains Attention to the exact chronology of the appearance of symptoms the appropriate management of the patient s interpretative delusions when such exist and a search for the subjective marks of systemic disturbances are therefore especially serviceable to the physician who is recording a patient s recollections

The totality of facts that the anamnesis can yield when it is skillfully elicited and recorded has an importance to the diagnostician in his appraisement of the physical psychical and social status of the patient under study that can scarcely be overestimated Both the anamnesis and the general physical and psychical examination are of course essential for clinical diagnosis and neither should be neglected I have heard more than one good clinician however, state that if they had to be guided by one or the other alone they would prefer to follow the path shown by anamnestic records that they had elicited rather than by the results of other examinations These were men however who through long experience had learned better how to assess the value of single subjective symptoms and groups of such symptoms than any beginner could hope to do Fortunately we do not have to be guided by the anamnesis alone or by the physical examination alone we utilize both to supply us with the symptoms and signs that clarify for us the diagnostic problem by which we are confronted But the point that I would emphasize here is that the facts obtained by recording the recollections of the patient form an indispensable part of the data we accumulate before we allow ourselves to consider the solution of any problem in clinical diagnosis

ad 2—*Recording of the Results of a General Physical and Psychical Examination* On making the general physical and psychical examination it is desirable to dictate the findings to a stenographer or to a stenotypist familiar with medical terms item by item as the examination proceeds for in this way only can a full objective record be obtained It is not safe to trust the results of such an examination even in so far as to attempt writing or dictating a report immediately after the examination has been made The examination involves so many details that one who attempts to make his records subsequently will often forget points of importance Moreover the record made later is pretty sure to be colored by the examiner s total impression derived from the examination and at this stage of the diagnostic study any such coloring is undesirable The examiner should make an

and immediately, place their hearts upon their sleeves for his inspection The larger the world experience of the physician, the greater his acquaintance with abnormal, nervous and mental states, the wider his sympathies, and the more winsome his personality, the easier it will be for him quickly to acquire the confidence of patients and an avowal of the sort referred to when it is desired for the purposes of diagnosis When the account given by the patient suggests the existence of abnormalities of the intellect, of the emotions, or of the will, it may be helpful also to interview, privately members of the patient's family or his business associates in order to learn what impressions they may have formed of the patient's nervous and mental state and what alterations if any in his personality they have observed By the prudent application of measures such as those described, the psychical social, and when necessary, the sexual status of the patient can nearly always be satisfactorily estimated and recorded

Besides the general features of the anamnesis above referred to there are certain special points that are worthy, perhaps, of particular mention One of these is the significance that sometimes pertains to recording the precise time relations of the appearance of different symptoms Thus when a tumor of the acoustic nerve developing in the cerebello pontine angle is present the exact chronology of the appearance of the different symptoms may be very helpful for the diagnosis And in other diseases (typhoid fever, malaria syphilis) the temporal relations of the symptoms may be informative A second special point in the anamnesis worthy of attention is the interpretation given by the patient himself of his illness as a whole or of any single symptom It is desirable to put such an interpretation down no matter how improbable or how erroneous it may seem to the examiner Every practitioner must have been impressed by the remarkable interpretation delusions that patients sometimes harbor But when the patient's explanation of his condition is obviously delusional some care must be taken to avoid too brusque a refusal of acceptance of his pathological interpretative ideas Only after confidence has been gained through a thorough investigation and through the establishment of a sympathetic relationship dare the practitioner hope to change such firmly set opinions Even then the bringing of conviction to the patient may not be possible except through a somewhat prolonged reeducative process A third matter that may well be again emphasized in the recording of the anamnesis is the extension of the questionnaire so that it shall certainly cover the marks of disturbances of the several anatomical physiological systems of the body If the several prominent symptoms mentioned in the above table be inquired about and the answers recorded it is not likely that many

anatomical physiological systems for regional examinations better permit one to accumulate facts without too much regard at the moment to their bearings upon the conclusion toward which the whole examination is aimed diagnostic inferences are to be avoided at this stage of the inquiry, suspension of judgment regarding the nature of the patient s ailment is at this time desirable One can scarcely with beginners in diagnosis emphasize too strongly this restraint of inference and suspension of judgment while the facts are being accumulated There is a great tendency among those who have never learned the importance and value of a general diagnostic survey to seize hold of some salient feature in the anamnesis or physical examination to allow it to dominate all of the further investigations and to permit it detrimentally to curtail the study of the patient as a whole Points of importance to be noted in the regional examinations are summarized in the accompanying table

B *Regional Examinations*

1 *Head* (skull face eyes ears nose mouth throat glands)
2 *Neck* (form thyroid tracheal tug esophagus blood vessels lymph glands cervical spine cervical ribs tumors wryneck)
3 *Thorax* (form bones coverings breasts axillary hirci and glands lungs pleurae and mediastinum heart and aorta)
4 *Abdomen and pelvis* (inspection percussion and auscultation of abdomen and abdominal viscera examination of rectum and of urogenital apparatus)
5 *Extremities* (skin bones joints muscles nerves)

After having made a record of the general points and of the points noted under regional examinations it is well even at this stage to make at least a general examination of the nervous system and sense organs in order that the data referable to the nervous system accumulated during the regional examination may be supplemented sufficiently to prevent us from overlooking data that point to lesions or to disturbances of function of the nervous system Points to be noted in this preliminary examination of the nervous system are summarized in the following table

C *General Examination of the Nervous System*

1 *Sensory functions* (cutaneous and deep sensibility stereognosis special senses including vision hearing smell and taste)
2 *Motor functions* (muscular power finer movements including speech and writing coordination tonus)
3 *Reflexes* (pupils deep reflexes of extremities superficial reflexes plantar and abdominal sphincters)
4 *Autonomic functions* (vasomotor secretory trophic)
5 *Mental state* * (orientation memory calculation attention sense deceptions pathological ideas mood psychogenic data etc.)

* If the exploration in this direction has been full enough and systematic enough in the recording of the anamnesis it may be omitted here

In making such a general physical and psychical examination we call upon our powers of clinical observation and of clinical experimenta

unprejudiced record of the findings in each region quite independent of any idea of what the ultimate diagnostic decisions are to be

Before undertaking the general physical examination the patient should be completely undressed and placed between sheets with a towel across the breasts, and the lighting arrangements should be such as to permit of satisfactory inspection How many errors in diagnosis would be avoided if practitioners always insisted upon the undressing of the patient before the examination is made! Many an aortic aneurysm many a breast tumor, many a hernia, many a bubo, and many a gibbus go unrecognized because of disobedience to this fundamental rule Where on account of prudery of the patient, or of great nervousness or of other cause a complete disrobing is not practicable, a note of this should be made in the record in order to call attention to the fact that the examination has been made under hindering conditions, later on, another examination can perhaps, be made under more favorable conditions, if it be thought desirable The patient should be under observation in good daylight the source of the light preferably being on the side of the patient opposite to that of the examiner For the valuation of pigmentations of the skin and of the conjunctiva, daylight is essential, for the rest of the examination good artificial light is permissible if daylight be unavailable Only when the patient's body is uncovered and adequately illuminated can one expect to make a satisfactory physical examination

When recording the results of the general physical and psychical examination it will be found convenient to subdivide the record into three parts A General points, B Regional examinations and C General examination of the nervous system and sense organs Thus the general points summarized in the accompanying table should first be recorded

A General Points

1 Body temperature pulse at both wrists respiration
2 Height weight calculated ideal weight build or habitus, acra nutrition musculature.
3 Posture gait behavior
4 Skin (color thickness moisture eruptions ulcers pigmentation scars striae nodules tumors superficial blood vessels edema)
5 Lymph glands (epitrochlear superficial and deep cervical occipital posterior auricular anterior auricular submaxillary axillary pectoral inguinal subinguinal popliteal)
6 Blood pressure (systolic diastolic)

Passing on to the exploration by regions, one examines, successively the upper extremities the head the neck, the thorax the abdomen and pelvis and the lower extremities There is a special reason for making the examination first mainly by regions rather than according to

pending the arrival of the records of results of laboratory examinations of X ray examinations and of examinations in special domains It is best to accumulate all this material before attempting to summarize the data and to rearrange them according to the anatomical physiological systems to which they may be especially related

ad 3—*Recording of the Results of the Application of Laboratory Tests* The methods of the clinical laboratory as developed in recent years yield data of real importance for clinical diagnosis When making a general diagnostic survey of a patient suffering from some obscure malady certain routine tests are now commonly made in hospitals and in the offices of consultants These include examinations of the blood of the sputum of the stomach contents of the feces and of the urine Just how much laboratory work shall be decided upon as a minimum routine requirement in every general diagnostic survey will vary with different clinicians There is a general tendency at present to have made as a routine in every case that is at all obscure unless for some reason one or more of them is contraindicated the laboratory tests mentioned in the following table

A Routine Laboratory Tests

1 *Examination of blood*
   - Red blood corpuscles count with notes on size and form
   - White blood corpuscles count.
   - Differential count of white blood corpuscles in stained smears
   - Platelets
   - Search for parasites
   - Wassermann reaction

2 *Examination of sputum* (especially for (1) tubercle bacilli and other bacteria and parasites (2) tissue fragments (3) spirals (4) elastic fibers (5) cells and (6) crystals)

3 *Examination of stomach contents*
   - Free HCl combined HCl and total acidity
   - Occult blood
   - Lactic acid
   - Oppler Boas bacilli

4 *Examination of feces*
   - Macroscopic and microscopic appearances
   - Undigested food (meat fats starch)
   - Occult blood
   - Bile.
   - Parasites or their eggs

5 *Examination of urine* (night and day specimens)
   - Physical (color reaction specific gravity)
   - Chemical (albumin sugar bile indican diacetic acid)
   - Microscopical (red blood corpuscles white blood corpuscles casts)

Some clinicians will be satisfied with a less comprehensive routine requirement and there are others who will desire a more extensive series of laboratory tests in every case But no matter what routine requirement one decides upon it is often desirable in special cases to have certain other laboratory tests made Thus when there are signs of

tion and these functions should be exercised in an orderly and balanced manner In simple observation we note and record conditions that we do not alter In an experiment we exert some influence upon the character of the event that we observe that is, our observations are then made under altered conditions Every clinical examination includes these two modes of experience long ago referred to by Herschel the astronomer, as "passive and active observation" The technique of clinical observation and experimentation has to be learned slowly In *our better medical schools the students are drilled in one method* after another until a certain amount of skill is acquired But the practitioner goes on increasing his skill as his experience grows The well trained and experienced practitioner can make a general physical and psychical examination, such as that outlined above, very quickly and accurately But even the well trained man should examine himself from time to time for tendencies to error One's methods of examination by observation and experiment are undoubtedly easily influenced by his special interests The making of an objective record of facts without bias is not easy, especially if they come into conflict with one s own peculiar views It is surprising how some men will always find tenderness at McBurney's point or in the right hypochondrium, how others will always find a few crackles in one interscapular space how others will nearly always find a vertebral spine out of alignment how others will suspect the existence *of a stricture of the ureter, and how others will always regard* a patient's feelings and behavior as psychoneurotic in type Men are very prone to find what they are looking for and it is easy to decide that very slight deviations from normal are worthy of being regarded as pathological findings if they be in the line of one's special clinical interests Minute and accurate observations are of course desirable but one must remember that the accurate recording of very minute deviations in one domain (the domain of one s special interest) if accompanied by failure of observation of grosser deviations from normal in other domains may result in an unbalanced study and in fallacious diagnostic inferences When several special examiners have coöperated with an internist in the clinical study of a patient it is of interest, when going over all the findings to see how often the special interests of the several collaborators have colored the record The observations and experiments made upon a patient should always be conducted with proper regard to a sense of symmetry and proportion for there should be in the clinical record a due and harmonious admeasurement of the parts to each other and to the whole'

The report of the general physical and psychical examination, after it has been typewritten, is placed along with the record of the anamnesis,

in diagnosis clinical laboratories have been so greatly multiplied and the number of persons professing to do expert clinical laboratory work has so greatly grown that it may be in place to sound a note of caution Unfortunately the sudden demand for laboratory tests has occasioned a supply of laboratories and of laboratory workers that contribute results of variable value Too often the work done is unsatisfactory Much harm can result from inaccurate reports emanating from unreliable laboratory workers Even the well trained worker in the best clinical laboratory will make a mistake occasionally in the performance of some test. Especially is this true of the Wassermann reaction Every effort should therefore be made to insure the avoidance of erroneous or inaccurate laboratory reports The value of a general diagnostic survey is not infrequently vitiated by an unwarranted credence in a laboratory report

It should further be emphasized that when practitioners call upon their co workers in the clinical laboratories for the making of special tests they should not expect the laboratory men to make their diagnoses *for them* They should ask for, and expect only reports upon the particular laboratory tests mentioned The results of these tests should be valued in association with the results obtained by other methods of examination It is only occasionally that a laboratory can report a result that is pathognomonic for diagnosis (positive Wassermann positive streptococcus culture or typhoid culture from the blood meningococcus or tubercle bacilli from the cerebrospinal fluid etc) One must remember too that even a pathognomonic finding by means of a laboratory test though it reveal the existence of a certain disease in a patient may not point to the pathological condition that is most important when the patient s whole state is considered A man may have syphilis and a glioma of his brain at the same time Another man may suffer from amebic dysentery and from leukemia at the same time The report of a positive Wassermann reaction in the blood in the one instance and the demonstration of the presence of amebae in the stools in the other though not to be underestimated in value would not point to the pathological conditions of paramount importance for the two patients mentioned Our diagnostic study in any given case should be comprehensive enough to include in the final summing up all the important deviations from the normal presented by the patient arranged in the order of their relative importance. But no attempt at the ultimate diagnosis of the case should be permitted at the stage of examination now under description The restraint of inference and the suspension of judgment that have been repeatedly emphasized should be continued until all of the data of our schema have been accumulated including

infection with continuous fever of unknown origin a blood culture will be made, but it is quite unnecessary to make a blood culture as a routine examination in every patient who presents himself A lumbar puncture with examination of the cerebrospinal fluid may seem desirable if a patient who has had lues years before presents nervous symptoms sug gestive of involvement of the cerebrospinal nervous system, or if in any patient there be signs of meningeal irritation, or if one suspect the existence of an epidemic encephalitis or of a Heine Medin infection, but it would be an unnecessary procedure to examine the cerebrospinal fluid as a routine measure in every patient who comes for examination. Again, if a peculiar arrhythmia present itself in the course of the regional examination, it may seem desirable to have polygraphic tracings of the radial and jugular pulse and of the movements of the heart s apex or an electrographic study though to apply the polygraph and the electrocardiograph to every patient in practice would be a waste of time and energy Laboratory tests in great variety have been devised but our clinical laboratories are gradually sifting out the less important ones and we are slowly becoming familiar with the best methods for securing the different kinds of valuable information that the clinical laboratory can yield Among the special laboratory tests occasionally required may be mentioned the following

B *Special Laboratory Tests* (to be made in certain cases)

1 Cerebrospinal fl id (lumbar puncture)
2 Tuberculin tests
3 Excision of a gland a piece of muscle or a nodule or making uterine scrapings for histological examination
4 Bacteriological smears and cultures (blood sputum urine pus prostatic milkings cerebrospinal fluid etc)
5 Blood chemistry and other special blood examinations (agglutinins lysins opsonins coagulation time bleeding time content in coagulation factors etc)
6 Renal function tests
7 Metabolic studies
8 Protein sensitization tests
9 Pharmacodynamic tests (with epinephrin pilocarpin or atropin)
10 Electrocardiography
11 Sphygmography
12 Exploratory punctures
13 Animal inoculations

Some practitioners especially young men recently trained in the medical schools make all of the laboratory tests required themselves Others make only their routine laboratory tests and depend upon special laboratory workers for the performance of the special tests Still others have all their laboratory tests made for them by assistants or by special clinical laboratory workers

Since the results of laboratory tests have come to be so highly valued

time and energy to roentgenological work The close association of the expert internist with the expert roentgenologist is essential to the highest quality of work of each The diagnostician who does not see the X ray plates on his own patients misses a great deal and the roentgenologist who is never able to control the results of his X ray examinations by the clinical history of the patient or by the physical examination made by the internist will fall into serious errors and will not grow as rapidly in X ray interpretation as he should Regular conferences should therefore be arranged between internists and associated roentgenologists

Altogether too much reliance is placed at present by many practitioners upon the reports in the form of diagnoses rather than in the form of concrete objective descriptions of their actual findings that are made by some roentgenologists The latter are perhaps not so much to blame for this as are the practitioners who pressingly solicit them to give specific diagnostic judgments based upon their X ray plates It may be very helpful of course to have the diagnostic impression of the experienced roentgenologist in addition to the objective description of his findings But the diagnostician making the general survey of the patient should be on his guard against accepting too readily the diagnostic impression of the roentgenologist The internist should pay much more attention to the objective description of the findings discovered by X ray methods than to such diagnostic impressions and should utilize these objective reports in connection with the data collected by all other methods in arriving at his diagnostic conclusion otherwise he will at times be led astray by a positive diagnosis ventured by the roentgenologist

General diagnosticians can in turn be very helpful to roentgenologists if they will report to the latter (1) the ultimate diagnostic conclusions to which they arrive after the study has been completed and (2) a summary of the data upon which the complete diagnosis is based We must gradually work out the methods by which roentgenology and internal medicine can be reciprocally most helpful If the internist and the roentgenologist will each give his best and if arrangements can be made for frequent conferences and discussions regarding the findings in concrete cases the accuracy of diagnostic studies requiring the coöperation of internists and roentgenologists will be rapidly advanced

When one is making a general diagnostic survey of an obscure case it is a real comfort to be supplied with the data that roentgenology can yield regarding the structures mentioned in the following table

those already referred to and those obtainable by X ray examinations and by intensive examinations in special domains

ad 4—*The Recording of the Results of X-ray Examinations* The X ray laboratory, like the clinical laboratory, has in recent times made important contributions to the methods of clinical diagnosis and is accordingly, now much appealed to for help in accumulating data regarding patients undergoing diagnostic study At first employed chiefly in surgical diagnosis the X ray laboratories to day are utilized even more by internists than by surgeons Many practitioners install a roentgenological department in their own office and do X ray work themselves or arrange for a roentgenological assistant Others send their patients to X-ray laboratories conducted by physicians who limit their work to roentgenology The great improvements that have been made in the manufacture of roentgenological apparatus have rendered the technique of X-ray examinations much more simple than formerly so that any intelligent person can be trained to make good roentgenograms of the bones joints teeth, lungs heart and aorta and alimentary canal The accurate interpretation of the roentgenogram is, however not such an easy matter In the first place no one but a medical man trained in anatomy, pathology, and the clinics can be expected adequately to interpret what can be seen in a roentgenogram, or what is visible on roentgenoscopic examination Even among medical men who devote their whole time and energy to roentgenological work the interpretative powers vary greatly, depending partly upon native endowment and partly upon length and intensity of experience. There can be no doubt that roentgenoscopic examinations and roentgenograms carefully made and properly interpreted are valuable contributions to the data with which the modern diagnostician should be supplied when he is studying obscure conditions

The importance of close cooperation between internists and roentgenologists is growing every day clearer An internist who to day is unable himself to interpret roentgenoscopic and roentgenographic findings is decidedly handicapped in his diagnostic work for even though he receive objective reports from competent roentgenological experts it will be hard for him to value these reports in a proportionate way Any clinician who has made an extensive study of X-ray plates and who has familiarized himself with what can be seen on a fluoroscopic screen will testify to the great autodidactic advantage that results from combining personal roentgenological interpretation with the results obtainable by other clinical methods Not that the hard working internist can expect to become as proficient in the interpretation of plates and screen views as are professional roentgenologists who give their whole

internist must ask himself what systems of the body of the patient require an especially intensive study and how the intensive study shall be conducted While taking the anamnesis and dictating notes on the physical and the psychical status of his patient the examiner will have had his attention arrested at intervals by the discovery of symptoms or signs that his experience has taught him are most frequently referable to disturbances of function in particular anatomical physiological do mains. Though in general restraining inference and suspending judg ment regarding the final outcome of his study the positively abnormal findings that have thus arrested his attention will serve as clues to sug gest certain special lines of inquiry they guide him to the domains that in the particular case merit a more thorough study than that made in the course of a general routine examination Thus the complaint of oppression in the chest on exertion or the observation of an increased blood pressure of an arcus senilis or of a cardiac arrhythmia may point to the desirability of an especially thorough study of the cardio vascular system In another case a history of recurring epigastralgia of gaseous eructations or of persistent constipation will lead the examiner to under take a special study of the digestive apparatus In another the history of frequent micturition during the night of difficulty in starting the flow of urine or of hematuria may make an examination of the urogenital system by special methods imperative Or again the presence of a polyarthritis will suggest to the examiner the importance of studying intensively all those domains of the body in which focal infections that may give rise to metastatic infections of the joints occur In such cases the question arises How shall this intensive study of special domains to which certain symptoms or signs point be undertaken? How can the data pertaining to these particular domains be most accurately most quickly and most inexpensively collected?

During the past fifty years the technical methods of diagnosis and therapy have been greatly enriched through that process of division of labor among medical men that we know as the rise of specialism in medicine Physicians and surgeons interested in special domains have devised a whole series of new methods of observation and of experiment some of them involving the skillful use of instruments of a greater or less degree of complexity The technique of ophthalmoscopy of re fraction of otoscopy of laryngoscopy of esophagoscopy of sigmoidos copy of cystoscopy of ureteral catheterization and the like can be learned by any medical man of intelligence but mastership in these practical technical procedures is not easy and requires a practical experi ence extending over a considerable time for its acquisition The result has been that many men have decided to specialize in order that they

Commoner Medical X ray Examinations

1. The paranasal sinuses
2. Dead teeth and unerupted teeth
3. The contents of the thorax (form size opacity or transparency)
4. The digestive tract as revealed in X rays during and after ingestion of barium (deglutition form size and motility of stomach and of different parts of intestine)

Roentgenograms of the paranasal sinuses and of suspicious teeth together with a roentgenoscopic report on the thorax and abdomen if made in the practitioner s own office can be done at very small expense so small that many practitioners could include the charge for such reports when made as a routine measure in the general consultation fee Only if the symptoms or physical signs point definitely to marked disturbance of the digestive functions or if in the absence of such symptoms and signs the roentgenoscopic examination done for eliminative purposes reveal suspicious findings, need the more expensive serial roentgenograms of the gastrointestinal tract be made The data obtainable by the simple and commoner X ray examinations enumerated in the above table go far toward protecting the physician who is making a general diagnostic survey of a patient from making certain sins of omission and commission that are frequent

In addition to such routine roentgenological examinations, certain special X-ray examinations may be indicated by the records of the anamnesis, by the results of the general physical examination, or by the preliminary roentgenological survey of the thorax and abdomen A list of the roentgenological examinations most often used is included in the following table

Special X ray Examinations (to be made when indicated)

1. Stereoscopic roentgenogram of skull of sella turcica or of mastoid portion of temporal bone
2. Stereoscopic roentgenograms of lungs and pleurae
3. Teleroentgenogram of the heart
4. Serial roentgenograms of the gastrointestinal tract
5. Roentgenograms of the gall bladder area
6. Roentgenograms of bones joints and spine
7. Roentgenograms for renal ureteral and vesical calculi
8. Pyelograms and ureterograms after thorium injection.
9. Ventriculograms after trephining and injecting air into the cerebral ventricles
10. Bronchiograms after insufflation of a bronchus with bismuth subcarbonate through the bronchoscope

One files the records of the results of any X-ray examinations made along with the other reports pending the collection of data derived from the intensive examinations of special domains that have become suspect from a consideration of the anamnestic and physical study

ad 5—*The Recording of the Results of Intensive Examinations of Special Domains* In making a general diagnostic survey an

specialties At present a young physician who desires to specialize in some one branch does best to attach himself as an assistant to a real expert in the subject that interests him Opportunities of this sort are of necessity limited in number It is owing to the paucity of such opportunities for intensive post graduate studies in the special branches despite the growing demand for specialists in practice that so much pseudo specialism now exists For the sake of the suffering public as well as for the advancement of scientific medicine this situation must be squarely faced by medical educators by philanthropists and by the state its defects recognized and the remedy sought and applied

The sick should reap the advantages that can be derived from the division of labor in medicine Laymen have discovered that some expert specialists exist but they are unable often to distinguish the true expert from the pseudo expert Having found that the general practitioner is not always wise enough to seek the aid of a true specialist when his help is needed laymen have tended more and more to apply directly to medical or surgical specialists when they themselves believe that their malady pertains to a special domain This tendency can only be harmful not only to the patients themselves but also to the general practitioners and in the long run to the specialists In order that the best work shall be done in diagnosis and therapy some means of coordinating the activities of general practitioners and specialists so that the best results will be obtained for all must be found A general practitioner or an internist who works alone and who does not call to his aid at least in an obscure case men who have had special training in particular domains will be sure to miss facts that are highly important for a complete understanding of his patient s condition On the other hand the specialist who works by himself taking care of all patients who apply to him whether or not they are referred to him by a general practitioner or an internist is in danger of forgetting that he studies only one part of the body and that though he may find abnormalities in his special domain these may be less important for the patient s whole state than are other abnormalities that exist unknown to him in other domains Some way or another must be found by which patients may profit by the division of medicine into specialties while at the same time they are protected from the dangers of a one sided study

The medical profession is now trying to solve the problem just stated by means of 'group work or cooperative diagnosis Diagnostic groups are being formed in which each member of the group possesses special skill in some particular kind of work and one member who acts as integrator tries to combine the single parts into a properly proportioned whole In this connection I can perhaps not do better

may acquire extraordinary skill in the diagnosis and treatment of disease in certain regions or systems of the body Thus, to day besides the general practitioner general internist and surgeon we see professional men who are known as specialists in diseases of children in diseases of the eyes, in diseases of the ears nose, and throat, in tuberculosis in cardio-vascular diseases, in diseases of the blood, in dentistry, in diseases of the digestive tract in gynecology, in urology, in orthopedics, in neurology, in psychiatry in dermatology, in endocrinology, in roentgenology, and in clinical chemistry No single person can therefore hope to be equally familiar with the facts and principles and equally skillful in applying the practical technical methods of all these specialties, indeed, few men pretend to mastery of more than two or three of them If the internist is to avail himself, then, of all the diagnostic methods that are helpful he must in certain cases at least, call specialists in particular domains to aid him by sharing in the labor of accumulating clinical data

Among the pressing problems that medical educators of the present time have to solve are those concerned with the training of both general practitioners and specialists and with the making of arrangements that will insure the mutual helpfulness of these two groups in the diagnosis of disease and the treatment of the sick The ordinary curriculum of the medical school is now so crowded that the medical student in his under graduate course, though he receives a thorough training in history taking and in the general methods of physical and psychical diagnosis can scarcely be expected to do more in addition than to learn the main facts and principles of the several medical and surgical specialties and to acquire enough first hand experience with special instruments like the ophthalmoscope the nasopharyngoscope the bronchoscope, the cystoscope the ureteral catheter the polygraph, and the electrocardiograph to permit him to understand their uses and to make clear to him the importance of their application as aids to diagnosis in certain special cases There is not time in the undergraduate medical course for the student to obtain the experience in any special domain that justifies him in regarding himself as a medical or surgical specialist. To become an expert ophthalmologist urologist orthopedist neurologist or dermatologist he must undertake special work extending over a con siderable period after his graduation The post graduate schools are attempting to supply opportunities for quickly gaining the experience in specialistic work that will make men competent but as yet only a beginning in this direction has been made There is urgent need for the endowment of post graduate schools with suitable hospitals attached in which men may be adequately trained in the work of the several

required special examinations in only one or two anatomical domains In obscure cases however and especially in instances of chronic infections necessitating the search for hidden foci we may feel the need of calling upon a number of experts for aid How many cases of chronic infectious arthritis for example progress for months because the diagnostic studies have been limited to too few domains when more complete studies might have located the primary foci that were responsible? No one can lay down hard and fast rules as to how extensive a study should be The judgment and experience of the one who has the general conduct of the study in charge must decide after the anamnesis has been recorded and the general physical and psychical examination has been made The main thing is that he who conducts the study shall be sensitive to the problems that confront him and know how to apply the best skill in attacking and solving them The greater the talents and experience of the integrator the better his insight and discernment the more likely he will be to have a proper sense of the indicative importance of the various features of a puzzling case The greater his familiarity with the making of general diagnostic surveys the more he will avoid requesting examinations that are wholly superfluous the less likely he will be to neglect a test that is essential in any single case The taking of too much pains in one case may be foolish the taking of too little in another may be disastrous

Just how such cooperative diagnosis will ultimately be carried out is as yet somewhat doubtful The general hospitals have been gradually working toward it but there must be much reorganization of these hospitals if the best results of cooperative diagnosis are to be obtained and especially the men working in such hospitals must be brought to an understanding of the advantages of such group work and must be taught how to organize for it and how the organization must be managed in order that it may be efficient Aside from the work of the general hospitals cooperative diagnostic clinics have already arisen in different places in the United States The Mayo Clinic at Rochester Minnesota and the 'Pay Diagnostic Clinics of Boston and of San Francisco are notable examples In many places group diagnosis is carried on in office buildings by coöperating physicians surgeons and specialists In most places however the physician making a general diagnostic survey still has to send his patients to specialists in his own town or even to those in more distant places for reports of intensive studies in special domains A general practitioner when isolated in the country has to do the best he can without such cooperative work and it has been matter of surprise and pleasure to me to see how successful some men so situated are in the general diagnostic surveys that they

than to quote from an address given before the New York Academy of Medicine in 1917, in which I briefly discussed this topic of cooperative diagnosis in obscure cases *requiring the intensive exploration of several* special domains

"The integrator should preferably be a person who, though perhaps especially skilled in some one branch is rather encyclopedic in training and comprehension, sympathetic and tolerably familiar with work in all the divisions of modern medicine and surgery, free from prejudices disciplined by sufficient experience in hospital wards in clinical laboratories and in the autopsy room and blessed with that common sense that is, in the last analysis, largely a sense of proportion

"Specialism thus resulting in the orderly cooperation of the members *of a group, instead of acting as a disintegrating force,* may be made to contribute to a higher unity, most helpful both to the public and to the profession With organization in groups of the kind mentioned it would matter but little to whom the patient applied for diagnosis, if the integrator be applied to first he will secure the reports from other members of the group before undertaking the integration, if a specialist in some single anatomical domain be applied to first, he may make his own examination refer the patient to the integrator for the conduct of the rest of the study, and receive from the latter the full and proportionate diagnostic report upon which a rational therapy can be planned *Obviously, mutual confidence and good will must prevail* among the members of such a group Such groups already exist and the number of them is, I believe destined rapidly to increase The older competitive methods must give way to the newer cooperative methods in medicine as in all other walks of life Nothing could be more unfortunate however than the formation of cliques when arranging for group work in diagnosis and I would warn emphatically against this danger It is obvious I think that such a system as I am referring to does not restrict any specialist or any integrator to activity in a single group, there is no reason why either should not participate in the activities of several different or overlapping cooperating groups the important points being that the group at work on any single case shall be so constituted as to insure first expert study in each of the several bodily domains in which there is an indication of the need of special study, and secondly a combination of the parts of the study into a well-balanced whole the systematic analysis being followed by an adequate synthesis

'Now in most cases there is of course no necessity of examination by every member of a large group of specialists In addition to the anamnesis the general physical and psychical examination the routine laboratory tests and X ray tests already mentioned there may be

more expensive diagnostic survey carried on in private wards of hospitals or in private clinics by an expert integrator cooperating with a group of consulting specialists Though groups of the latter sort study a certain number of patients of small or of moderate means reducing the fees charged for the whole study to an amount that is no hardship or inconvenience to the patients no matter what their incomes are still the amount of such work that can be done by the groups thus far organized is relatively small in proportion to the public need Moreover many patients who would benefit by a general diagnostic survey hesitate to avail themselves of an organization in which the ordinary charge for a general study is beyond their means, even though the total charge be willingly reduced to a merely nominal sum In Boston and in San Francisco an effort has been made to provide for this class of patients in the Pay Clinics that have there been organized and at the Mayo Clinic the cost of an elaborate general diagnostic study has been kept low There would seem to be room in all large cities for organizations of young men who are gradually making their reputations to be of service in this connection This is work too for which community funds justifiably might be expended Industrial establishments towns cities counties and states might do well to foster organizations for group diagnosis making financial appropriations to aid them and providing for regulation and supervision that would insure efficient and ethical conduct The methods of the business organizer and business manager might well be adopted here not for exploitation but for the welfare and protection of the sick

The filing of reports of the results of intensive examinations of special domains completes the preliminary collection of data necessary for the localization and definition of the diagnostic problem The facts accumulated include the records of the anamnesis of the general physical and psychical examination of the laboratory tests made of the X ray tests made and of the intensive examinations made in special domains These facts may now be summarized and arranged in groups according to the anatomical physiological systems to which they pertain The time will then have arrived for brooding over the data gathered and for allowing the things that we have observed to bring into our minds things that we have not observed Suggestions of solution of the diagnostic problem ought to begin to occur to us We are ready therefore to enter upon the third stage of the diagnostic procedure

make Certainly recent medical graduates, who have had a thorough training in general medicine surgery, and the more important medical specialties as well as in laboratory work and in X ray work, may, single handed, do general diagnostic work of a very high order before they become too busy though even these men could do still better work if they were members of groups in which a division of labor was arranged for It seems to me possible that in country districts, county hospitals in which the work of cooperative diagnosis by a differentiated staff will be undertaken and be supported in part by public funds may ultimately be organized Great convenience for patients and for physicians results from arranging for the combination of the differentiated diagnostic activities under a single roof Centers in which cooperative diagnostic groups can work effectively seem destined to grow in numbers and in public esteem

The cost of making a complete diagnostic survey in an obscure case requiring the cooperative activities of a general internist and a group of specialists is an item that merits special comment Unless ways can be devised for bringing the cost of such an examination comfortably within the means of all that require it many who would benefit by it will be compelled to do without it It must of course be borne in mind that the great bulk of medical practice as done at present is carried on without the making of a general diagnostic survey of the patients in the sense of this discussion Indeed for the host of minor ailments from which patients suffer it would be superfluous to undertake the kind of general diagnostic survey here described An elaborate investigation of every minor ailment would be a waste of the patient's time and money and of the physician's time and energy Among his patients the physician of good judgment will have but little difficulty however in selecting a certain number that for their own sake as well as for the reputation of the practitioner, should be advised to undergo a general diagnostic survey Those selected would include the class of patients ordinarily referred to internists surgeons and medical and surgical specialists for consultation For this group of cases it is desirable that methods for making quickly efficiently and inexpensively a general diagnostic survey shall be evolved Thus far the well to do are becoming provided for in the private wards of general hospitals and in private group clinics and the poor are also being very well looked after in the public wards of those general hospitals in which the method of group diagnosis has been introduced Provision has yet to be made however for satisfactory group diagnosis for those patients whose incomes preclude the use of free dispensaries or of the public wards of hospitals but are not sufficiently large to permit them to pay the usual fees for the

anatomical physiological domains to which they reasonably may be supposed to be related This is another method of finding out whether our observations and experiments have been sufficiently inclusive For this rearrangement of the facts in a systematic way I myself make use of a single sheet upon which the following form is printed sufficient space being provided for the inclusion of the various symptoms and signs that are likely to be met with in any case in connection with any one of the anatomical physiological systems

Data Rearranged According to the Systems to Which They May Be Related

Name **Age** **Body Temperature**
Chief Complaints
Time and Mode of Onset
Habits
Infections
Operations Traumata
Respiratory System
Circulatory System
Blood and Hematopoietic System R B C Hb W B C WaR.
PMN PME. SM LM Tr
Platelets Bacteria Parasites
Digestive System Free HCl Total Acidity Occ Blood Stool
Urine and Urogenital System Urine Sp gr Alba Sugar Cyla
W B C R. B C Phthalein Output
Locomotor System
Nervous System and Sense Organs
Metabolism and Endocrine System
Remarks

In this systematic rearrangement of the more important data we include both positive and negative findings jotting them down in as brief form as is compatible with quick apprehension use being made of various symbols for purposes of abbreviation Thus under the heading Circulatory System' will be placed symptoms such as dyspnea palpitation precordial pain and retrosternal oppression should they be complained of any physical signs referable to the heart and blood vessels (e g pulse rate arrhythmias systolic and diastolic blood pressure position and character of apex beat abnormal pulsations heart murmurs cyanosis thickened vessels arcus senilis or edema) teleroentgenographic measurements and electrocardiographic results if they have been recorded Under the heading Metabolism and Endocrine System' will be placed deviations from calculated ideal weight notes from the anamnesis regarding gouty attacks or a gouty family history diabetic symptoms struma tachycardia fine tremor eye signs common in the thyreopathies abnormalities in the distribution of hair pigmentations condition of the acra and the like When placing a symptom like dyspnea it may be well to include it not only under Respiratory System but also under Circulatory System and under Metabolism unless it has already become clear to what division the symptom predominantly belongs Each integrator in rearranging the data will

Stage III Summarizing and Arranging the Data Accumulated, Pondering Them and Recording the Diagnostic Suggestions That Occur to the Mind

In order that suggestions of possible solution of our diagnostic problem may occur to our minds, we must weigh mentally the facts that we have accumulated in recording the anamnesis in making the general physical and psychical examination, in the making of laboratory tests and of X ray tests and on intensive examination of special domains We stop observing and experimenting for a time in order that there may occur to us ideas of what the things already observed may mean We begin to draw inferences from the facts

Consideration of the facts with this purpose in view is greatly facilitated however, (1) by making a preliminary summary and (2) by rearranging the facts in a systematic way

Thus, in order that one may take in at a glance the positive abnormal findings in the case, it will be found convenient first to summarize these findings under the general headings that correspond to their mode of accumulation

Summary of Abnormal Findings

1 Anamnesis
2 General physical and psychical examination
3 Laboratory tests
4 Roentgenological examinations
5 Intensive examinations in special domains

From the large mass of data accumulated one selects for this preliminary summary only the points that represent definite deviations from normal conditions This makes for brevity and for ease of survey, and the summary serves as a valuable control of the fact accumulation for one can from looking over it quickly discover whether any important method of examination suggested by the results of the anamnesis and of the general physical and psychical examination has been omitted in the study as carried on up to this point Furthermore when the more important facts are thus closely crowded together in a summary, defects in the reports of suggestive symptoms or of physical findings or of special examinations may be easily recognized and remedied before one entertains ideas of interpretation One may find for example that the report of a dental consultation, or of an X ray examination that has been requested has not been sent in, or one may on this quick review become cognizant that he has neglected on outlining the course of the study to include the making of some observation or of some special test the necessity for which was clearly pointed to by one of the symptoms of which the patient complained or by one of the signs recorded at the first physical examination

The data accumulated may next be rearranged according to the

by induction or by deduction to inference We brood over the materials that we have selected and prepared in the hope that things that we have observed will lead us to ideas of things that cannot be observed Contemplating the contents of our experience with the patient before us we try to assimilate them with the contents of our own past experience (gained by studying patients and the medical sciences) and of the experience of other physicians as reported to us in medical literature believing that on such assimilation suggestions will arise in our mind that we may tentatively entertain concerning things that our own present experience by itself, does not hold In other words we now call upon our powers of reflection to make contributions beyond what our sense organs are able to yield to us Were it not for this capacity of the mind to make leaps from facts to ideas we should never go far in the process of clinical diagnosis The mind of the diagnostician must bound forward by a leap or by a succession of leaps from the observed clinical facts to ideas of what *these facts may mean* Thus *the integrating internist* must be a mental gymnast and he has to learn that expertness in the form of intellectual activity here described can scarcely be expected except after long experience carefully directed The regulation of the conditions under which the function of suggestion is allowed to take place is of the highest importance Unless due care and attention have been exercised in the accumulation selection and arrangement of the facts from the consideration of which the diagnostic suggestions are to emerge the conditions under which the creative imagination has to work will be faulty Even when the conditions have been adequately regulated a proper use of the function of suggestion implies the cultivation of both courage and caution as habits of mind We should be bold enough to entertain several rival diagnostic *conjectures* that we test for validity but we must be cautious enough to make sure that only hypotheses that are found on testing them to be valid are accepted as diagnostic conclusions One sometimes hears medical men well meaning enough but innocent of any real acquaintance with the manner of working of the mind of the scientist declare that there is no place for imagination or for hypothesis in diagnostic work and that the real diagnostician should content himself with facts But the truth is that everyone who does good work in clinical diagnosis is compelled whether he is cognizant of it or not to form hypotheses before he arrives at satisfactory diagnostic conclusions A study of the conditions under which hypotheses should be permitted to arise and a knowledge of how to deal with these hypotheses once they have arisen in the mind would seem then to be indispensable for the higher walks of clinical diagnosis

adopt or devise symbols and abbreviations that, though they are immediately intelligible save space

It will have been observed that, in making such a systematic rearrangement of the findings, the integrator has already begun to draw certain inferences and to make a series of particular judgments, for the assignment of given symptoms or signs to definite anatomical physiological domains is based upon knowledge or prior experience concerning the possible meanings of those symptoms or signs The actual process of clinical diagnosis includes a search for clues or marks and the formation of judgments regarding the meaning of such clues or marks as are discovered The rearrangement of these clinical marks in groups according to the several anatomical physiological systems to which they presumably pertain takes the facts out of the quarantine hitherto imposed upon them isolation of the single facts gives way to association in groups as the integrator works at this stage of the diagnostic procedure The materials thus dealt with prepare the way for the perception of further relations that may exist among the facts Thus the data pertaining to each anatomical physiological domain may next be considered as a whole and judgments formed concerning their meaning and origin, later on, the relationship of the disturbances discovered in one anatomical physiological domain to those found to exist in other domains may be sought for with the idea of uniting two things in a third that is the foundation of the relationship (*fundamentum relationis* of the schoolmen) Such partial considerations as those just mentioned are necessary preliminaries to the localization of disease processes, and the assignment of place to the pathological phenomena is, in turn, necessarily antecedent to a proper understanding of the nature and cause of these phenomena reflection upon the state of the patient as a whole which we depend upon for supplying us with suggestions regarding the ultimate solution of our total diagnostic problem, can be advantageously entered upon only after we have made a long series of partial considerations and particular judgments and have already surmounted a number of local and minor diagnostic difficulties

It may be worth while to advert for a moment to the kind of mental process we make use of when we have reached the stage of our diagnostic investigation in which we allow ourselves to entertain suggestions of explanation of the data that we have gathered summarized and systematically rearranged We begin now to draw larger inferences to form diagnostic hypotheses to harbor interpretative ideas Observation and experimentation, hitherto our main tasks are now temporarily stopped We begin to think and to make use of the creative imagination With feet firmly fixed upon a basis of the facts observed we try to pass

wondering whether this disturbance had its origin in some organic lesion within the heart itself or had been due to a depression of the function of the bundle through vagus influences excited from a distance (intestinal irritation increased intracranial pressure)

If to take another example under the Urogenital System in a woman of forty two one find recorded a prolonged metrorrhagia say a flow of ten days each month along with enlargement of the uterus he will probably think of myomatosis with endometritis and of carcinoma uteri as rival explanatory hypotheses each of which is rigorously to be tested for validity If under the Nervous System the data include nystagmus loss of abdominal reflexes and scanning speech the integrator will think at once of lesions disseminated through the nervous system the exact topography and nature of which he may try to determine Or if under the Hemapoietic System he finds jotted down a profound anemia with leukopenia with a differential count of the white corpuscles showing a relative lymphocytosis of 94 per cent along with enlargement of the spleen and with slight enlargement of the cervical lymph glands the experienced internist may think of the possible existence of an aleukemic lymphadenosis of a pernicious anemia or of an anemia occurring in the course of a syphilis As these examples illustrate we deal at this stage separately with the symptoms and signs that pertain to each one of the several anatomical physiological domains cudgeling *our brains for cues of possible meaning When a group of* signs and symptoms are present in a single domain one should not be too easily satisfied with the occurrence to the mind of a single descriptive or explanatory hypothesis Several possible hypotheses should be allowed to present themselves if they will and these should be pitted against one another as lusty rivals that are to be given opportunity to fight for supremacy Hundreds of examples of syndromes might easily be given were there need but those mentioned will doubtless suffice to illustrate the mode of occurrence of diagnostic ideas to a mind that is pondering the symptoms and signs that have been referred to a given anatomical physiological system

As has been repeatedly emphasized in this article on encouraging diagnostic suggestions to which a consideration of the facts as summarized and rearranged is to give rise one tries to make scientific use of the imagination a process that makes demands not only upon the intellect but also upon the affective conative functions (the feelings and the will) From one s previous knowledge and experience he attempts to recognize in the group of facts before him either some well known uniformity of sequence or some easily identifiable uniformity of coexistence only when no well known one can be discovered by him

Returning now to the actual occurrence of diagnostic suggestions to the mind when studying given cases, we may illustrate, by citing a few examples how suggestions of meaning begin to arise on looking over the groups of symptoms and signs after their systematic tabulation in groups corresponding to single domains Thus, if one finds recorded under the ' Digestive System " morning diarrhea and the absence of free hydrochloric acid in the stomach juice, he will at once think of an achylia gastrica and of its possible relationship to a chronic gastritis to an oral sepsis or to a pernicious anemia Or if under the same system one finds recorded a gastric hyperacidity tenderness in the right lower quadrant displacement of the stomach markedly downward and to the right in the roentgenogram and the history of recurring attacks of indigestion he will think of the possible existence of some lesion in the right lower quadrant of the abdomen say a chronic appendix Or if there be recorded in an obese person above the age of 40 a gastric subacidity a history of pain in the right upper quadrant of the abdomen (especially after riding horseback, after a night's ride in a sleeper, or after an automobile tour) of transitory attacks of jaundice and of an earlier attack of typhoid fever the idea of some gall bladder trouble probably gall stones will occur to the mind Or if one find recorded anorexia an absence of free hydrochloric acid in the stomach juice occult blood in the stool and a definite filling defect in the roentgenogram of the stomach the existence of carcinoma ventriculi will at once be suspected Or again, if under the ' Circulatory System " one sees noted a retromanubrial dullness a systolic blood pressure of 170 a diastolic pressure of 90 thickened radial arteries an arcus senilis a widened aorta or a transverse position of the heart in the X-ray he will think at once of an arteriosclerotic process, or if a definite thrill be palpable in the region of the apex of the heart and an asynchronism of the second sounds be audible in the pulmonic area, the first sound at the apex being abrupt the existence of a mitral stenosis due to an earlier thrombo endocarditis will no doubt suggest itself as a diagnostic idea Or, if at the wrist a perpetually irregular pulse be felt and the record of the electrocardiogram shows a good many small waves arising in the atrium for every ventricular complex the existence of atrial fibrillation will at once be thought of and a search for its etiology suggested Or if the pulse rate be 120 and there be no heart murmurs or marked enlargement of the heart one will think at once of the possibility of a thyreopathy as an explanation and seek for corroborative data Or if again the pulse rate be 48 one would leap to the idea of the existence of a conduction disturbance in the atrioventricular bundle of the heart and would also find himself

wondering whether this disturbance had its origin in some organic lesion within the heart itself or had been due to a depression of the function of the bundle through vagus influences excited from a distance (intestinal irritation increased intracranial pressure)

If to take another example under the Urogenital System in a woman of forty two one find recorded a prolonged metrorrhagia say a flow of ten days each month along with enlargement of the uterus he will probably think of myomatosis with endometritis and of carcinoma uteri as rival explanatory hypotheses each of which is rigorously to be tested for validity If under the Nervous System the data include nystagmus loss of abdominal reflexes and scanning speech the integrator will think at once of lesions disseminated through the nervous system the exact topography and nature of which he may try to determine Or if under the Hemapoietic System he finds jotted down a profound anemia with leukopenia with a differential count of the white corpuscles showing a relative lymphocytosis of 94 per cent along with enlargement of the spleen and with slight enlargement of the cervical lymph glands the experienced internist may think of the possible existence of an aleukemic lymphadenosis, of a pernicious anemia or of an anemia occurring in the course of a syphilis As these examples illustrate we deal at this stage separately with the symptoms and signs that pertain to each one of the several anatomical physiological domains cudgeling our brains for cues of possible meaning When a group of signs and symptoms are present in a single domain one should not be too easily satisfied with the occurrence to the mind of a single descriptive or explanatory hypothesis Several possible hypotheses should be allowed to present themselves if they will and these should be pitted against one another as lusty rivals that are to be given opportunity to fight for supremacy Hundreds of examples of syndromes might easily be given were there need but those mentioned will doubtless suffice to illustrate the mode of occurrence of diagnostic ideas to a mind that is pondering the symptoms and signs that have been referred to a given anatomical physiological system

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does he permit himself to think that he may be dealing with some new, or hitherto undescribed, syndrome The aim of every scientific worker is to discover scientific laws to which the facts that he accumulates will conform The scientific diagnostician desires also to summarize in a single statement, or in some brief formula, the disease process by which he is confronted and from which the whole group of facts that he has collected regarding the patient can be seen to flow Out of a vast complexity of anamnestic data of physical signs, of chemical reactions, and of biological tests he strives to derive a unity to detect the "one in the many" by means of a disciplined imagination he attempts to formulate conceptions in which the whole range of facts may be resumed He sets up groups of tentative or hypothetical conclusions that he is to scrutinize thoroughly and to examine adversely before admitting their validity In order that a clinician may make a diagnosis as complete and as satisfactory as is possible in the state of medical knowledge that exists in his time he must obviously, in addition to native ability, have a wide acquaintance with the main facts of all the medical sciences and he must have already become familiar with the classifications of groups of facts and with the descriptive formulae that have hitherto been made use of by other clinical workers A certain esthetic element doubtless enters into the experience The brief statement under which a large number of facts or of perceptions and conceptions is resumed must be felt to be adequate

It was Karl Pearson I believe, who emphasized that the continual gratification of the esthetic judgment is one of the chief delights of the pursuit of science That this is true in the science of diagnosis will be admitted by every advanced worker The more comprehensive the diagnostic study made and the more complete the understanding of the relationships of alterations of form and function to causes arrived at the greater the esthetic appeal to the mind of the diagnostician of philosophic turn This is why he in making a clinical diagnosis strives to arouse satisfactory suggestions of solution of his diagnostic problems by thinking systematically first, of the possible pathological physiological significance secondly of the possible pathological anatomical basis and thirdly of the possible etiological and pathogenetic relationships of a given fact or group of facts He thus secures his ideas of syndromes made up of functional disturbances, of the lesions present and their topographical relationships of the nature of the disease processes that are going on in his patients and of their etiology The several ideas that thus occur to him must he knows be subjected to such rigid criticism that the conclusions he finally arrives at will be equally valid for the minds of other clinicians who

work in the same way Intellect emotion and will—all contribute their share to the mental operations of this stage of the diagnostic inquiry

One may ask the question What reason have we to believe that different physicians even when using the method of science will in studying a given case arrive at similar, or identical diagnostic conclusions? The reason why there can be and often is agreement in opinion among diagnosticians lies one must believe in a similarity of behavior of normally constituted minds To the normal mind the world outside—the world of phenomena—presents itself in a certain way The perceptive powers of normal minds must be very similar to one another The same must be true of the reflective activities of the mind in normal persons The mechanisms of association and of logical inference work similarly in different healthy people with the result that the mental contents of stored sense impressions and of conceptions will be sufficiently similar to yield almost identical results in the same circumstances The normal mind when bombarded by a series of sense impressions or perceptions associates them with sense impressions that have been stored in the memory it combines these into conceptions or constructs a train of thought is set up through association and the recognition of relationships, conceptions are formed and inferences begin to be drawn Were it not that normal human beings perceive the same phenomena and reflect upon them in very similar manner there could be no agreement regarding diagnostic conclusions indeed there could be no such thing as science of any sort As Pearson has well put it 'Human minds are within limits all receiving and sifting machines of one type' Minds that in their activities deviate too much from this normal type we call disordered or insane Within the range of normality however there is opportunity for considerable variation in activity Minds that we call normal though very similar in their activity are by no means identical We have abundant proof of this in the diagnostic suggestions that occur to different physicians who have had similar training and equality of opportunity for acquiring experience To one mind ideas of meaning may come easily and promptly to another they come slowly and with difficulty To one mind a group of facts may quickly give rise to several ideas of possible meaning to another mind the stimulation by the same group of facts is barren of response It is desirable of course that the number and range of ideas excited by the facts accumulated will suffice for the purpose of the study there should not be too few of them and there should not be too many Moreover the quality of the ideas of solution that are aroused is even more significant than the promptness with which they come or the abundance of the supply One physician s mind may respond speedily with an abundance

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ranged no matter how plausible such a suggestion may seem it should have been traced to its full consequences and its validity carefully tested The acceptance of an idea as valid before it has been elaborated so that its full bearings may be clearly seen and compared with the facts that exist is the mark of an uncritical thinker There is no room in clinical diagnosis for light hearted and over ready belief Any tendency to infer wildly rashly or fallaciously must be vigorously combated One should familiarize himself with the canons of legitimate inference and make sure that he is governed by them When resorting to this reasoning process in which all the implications of each suggestion deemed worthy of testing are developed and are compared with the facts that have been accumulated regarding the patient it will frequently occur that the diagnostician will discover the need of supplementing his first store of facts by further observation or by further experiment It may even be necessary to apply methods other than those that have been used in a search for new materials to support or to render untenable an idea of interpretation that has occurred to the mind It is only after we have entirely unfolded a diagnostic idea in detail that we can compare the several particulars that compose it with the facts as we have observed them and decide whether or not sameness can be recognized and identity established When the facts observed are found to be in accord with the implications of a diagnostic suggestion as fully reasoned out we accept the suggestion as valid and have a feeling of belief in it

This process of developing the implications of diagnostic suggestions by reasoning may be illustrated by considering as examples the diagnostic suggestions that occur to us as solutions of the diagnostic problem presented by a patient who exhibits an acute febrile process with leukopenia The patient let us say has complained of headache of pain in his back of loss of appetite and of disinclination for exertion The temperature of his body has been found to be 102 5° Fahrenheit his pulse rate is 84 and the pulse is slightly dicrotic A few rhonchi are audible over the lungs the spleen is palpable and the white cell count of the blood is 4 800 When confronted by this group of facts the diagnostician will at once think of infectious processes associated with splenomegaly and leukopenia and he will recall that two of the commoner infections of this sort are typhoid fever and malaria. His next step will be *to develop the implications of* each of these two diagnostic suggestions by reasoning He will say to himself If the suggestion of typhoid fever be correct we should find in studying the history of this patient s illness an insidious onset of the symptoms a characteristic temperature curve a relative bradycardia an initial bronchitis headache anorexia palpable spleen perhaps rose spots a leukopenia an

of suggestions and yet these suggestions may be inferior for the purpose in hand to those that arise in a mind whose response is slower but more profound Rapidity of response is of course good in itself, but mere quickness will not compensate for either excessive prolificity or superficiality A physician should as far as possible, train his mind to make quick balanced and deep responses when he contemplates groups of clinical facts in order that he may be supplied with enough worthy and substantial diagnostic ideas to test systematically for validity Good native ability and prolonged training are essential for the best kind of diagnostic work Though minds differ, the differences within normal limits are less important than the resemblances Normally constituted minds are so nearly alike in their workings that diagnosticians of normal mental endowment who are well educated in the contents and methods of the medical sciences, on studying similar pathological conditions will we may feel sure arrive at similar conclusions

In making a general diagnostic survey of a patient the aim is to get as complete an understanding as possible of the functioning of the whole man in his physical psychical, and social aspects with the object of being of real help to him in improving his condition As has been pointed out the group of facts pertaining to each of the bodily domains (respiratory, circulatory, digestive etc) is first appealed to for suggestions of meaning and for calling forth in our mind ideas of similarity, of coexistence or of sequence We should not stop however, with the recording of suggestions based upon the consideration of the data pertaining to these several systems but should next turn to a survey of the whole series of suggestions that have thus arisen For after testing systemic ideas for their validity we want to know the relative importance of the several partial diagnoses that are found to be valid for an understanding of the condition of the patient as a whole Until this general survey has been undertaken and completed no final unified diagnostic conclusion with suitable ordination of all the factors in the case can be arrived at By keeping the purpose of the diagnostic study vividly in mind namely the desire to find out what is wrong with the patient, in order to direct him how best to act, we shall find a suitable guide to the whole diagnostic procedure this directing principle will enforce orderliness in the application of our methods and it will give steadiness and continuity to our thinking as it moves toward its goal

Stage IV The Elaboration by Reasoning of the Implications of Each Diagnostic Suggestion or Inference

Before yielding assent to any suggestion that has issued from a consideration of the facts after they have been summarized and ar

the idea of tabes dorsalis at once simply because an Argyll Robertson pupil is not present but will still keep this diagnostic suggestion in mind along with other conjectures of possible solutions of the diagnostic problem (funicular myelitis, polyneuritis etc) He will then reason each of the suggestions out fully as to its implications and if necessary will make further observations or experiments that will decide whether identity exists He may require to extend the blood examination to undertake the examination of the cerebrospinal fluid or to map out the exact topography of the sensory disturbances It may even be necessary considerably to enlarge the anamnestic record in the case If there be no anemia if the cerebrospinal fluid yield a positive Wassermann reaction and contain many lymphocytes and more globulin than normal if the topography of the sensory disturbance be segmental in type and if the revised anamnesis reveal the history of luetic infection of periods when lancinating pains occurred and show the absence of any abuse of alcohol and of any poisoning by lead arsenic or other substances that cause neuritis the idea of tabes dorsalis as a satisfactory diagnosis may be accepted as valid even though no Argyll Robertson pupil be demonstrable Thus a diagnostic suggestion that on elaboration seems to be inconsistent with some of the data present may on modification be found to be adequate as a solution of a diagnostic problem

The original diagnostic suggestions that come up in our minds are always inchoate, they require to be developed From principles that have already been established in medicine and with which we have become familiar through our earlier clinical experience and through our study of medical books and journals we deduce the fullness and completeness of their meaning The data accumulated by the analytical processes of the anamnesis and by means of the general physical and psychical examination the laboratory tests the X ray tests and the special tests suggest to us when we brood over them wholes into which they may be synthesized Such suggested wholes are then again disintegrated by a reasoning process of deduction into their known constituent parts Further observation and experimentation may then be required before identity can be established between one of these suggested wholes with its constituent elements and the actual whole to which the symptoms and signs in our patient really belong Indeed one of the great advantages of the consideration of all the possible bearings of the general diagnostic notions that we tentatively harbor i that it often leads us to expand substantially our collection of particular data The full development by reasoning of all the implications of the diagnostic suggestions that occur to us is then an essential part of the diagnostic procedure

early bacillaemia an absence of coryza and herpes an epidemiological record that gives the clue to the source of a bacillus typhosus in the case, the presence of the typhoid bacillus in plate cultures made from the feces on the Drigalski Conradi medium or on Endo's fuchsin agar the presence of specific agglutinins in the blood after the disease has lasted for a certain length of time, etc" He will also elaborate the suggestion of malarial fever and will say to himself, ' If this patient has malaria his temperature chart should be that of either an inter mittent fever (if it be a tertian or a quartan case), or a continuous or remittent fever (if it be an estivo autumnal case), the patient will have had chills sweats headaches anorexia palpable spleen herpes labialis leukopenia, anemia a history of exposure to the bite of an *Anopheles* mosquito and perhaps neuralgic pains, in his blood the presence of malarial parasites should be demonstrable and pigment containing leukocytes may also be discernible, marked amelioration of the symp toms will follow the administration of quinine, etc" If the diagnos tician be a careful and experienced worker, he will have thought not only of the commoner infections associated with leukopenia such as typhoid fever and malaria but also of the somewhat less common con ditions so associated such as paratyphoid fever measles mumps glanders and dengue It will have occurred to him still further that *leukopenia is sometimes met with in certain very severe forms of* infec tion like pneumonia and septicemia that in ordinary circumstances are associated with leukocytosis He will then develop the full implications of these diagnostic ideas also These several diagnostic suggestions thus fully developed as to their implications will be looked upon by him as so many intellectual keys with which he will successively try to fit the lock

If none of the keys he has forged is found to fit he must try some modification of one of them or make still other keys to try It may be that some complicating process of a secondary nature is changing the clinical picture so that it deviates from type When in a case a survey of the data as a whole suggests the existence of a certain disease process one should give this process careful consideration even though some of the data recorded seem to be inconsistent with it Thus if the symp toms and signs on the whole suggest the existence of typhoid fever one should not throw this diagnostic suggestion into the discard simply because a leukocytosis is present, for although leukopenia is the rule in typhoid fever, we do sometimes find a leukocytosis in that disease owing to a complicating pyogenic process (phlebitis pneumonia chole cystitis etc) Or to take another example, if the knee-jerks and ankle jerks are absent in a patient and anesthesias and paresthesias of his lower extremities have been recorded the diagnostician will not rule out

paring the whole meaning embodied in the diagnostic suggestion that is the whole of the consequences that flow from it, with the actual clinical facts that we have gathered or that we can gather by further observation and experimentation We have at this stage to trace out fully the degree of similarity that obtains between the facts that exist and the facts that should exist if the ideas that have occurred to us are true We must ascertain whether there is a sufficient degree of likeness or sameness to justify the acceptance of the idea that we have tentatively entertained and rationally elaborated and if we have provisionally considered other diagnostic ideas as rivals to it we must demonstrate that the distinguishing criteria of these rivals are absent Unless a diagnostic idea as fully reasoned out can be verified we dare not believe it to be true

The secondary observation and experimentation stimulated by our attempt to establish identity between observable particulars and the implications of a tentative idea may strengthen or weaken the diagnostic conjecture and result in corroborating it or in refuting it. Thus in the case of infection with fever, leukopenia and palpable spleen to which we have referred it may be found possible on reexamination of the patient to discover that we had previously overlooked a roseola or we may find on the patient s lip a slight herpes that had not been noticed at the first examination or that had been passed over as insignificant or in a blood culture made in bile bouillon we may be able to grow a motile bacillus which on being tested turns out to be the bacillus paratyphosus, or again on making another careful search of a stained smear of the blood we may find a single crescent shaped malarial parasite or some small intracorpuscular forms that earlier had escaped observation or a week or two after the first examination during which time the diagnosis has remained in doubt we may become able to demonstrate specific agglutinins for bacillus typhosus in the blood though the Widal reaction had been negative at the first examination Thus where neither corroboration nor entire rejection may be justifiable on comparison of the facts originally collected with the implications of the conjectural idea of diagnosis entertained additions that will bring a decision may sometimes be made to the clinical data

As long as the data are insufficient for the determination of identity between the facts of experience and the reasoned out implications of a diagnostic idea the scientific diagnostician will reserve his judgment And though doubt as to diagnosis will seem intolerable to him as long as a chance of a justifiable decision remains open he will nevertheless often be compelled to suspend a conclusion when a more ignorant or a less cautious mind unwilling to bear a painful feeling of incapacity

Stage V The Testing of Diagnostic Suggestions (Elaborated by Reasoning) for Their Validity and Arriving at Diagnostic Conclusions or Beliefs

It has been repeatedly emphasized that before we accept a diagnostic suggestion, inference, or hypothesis, after developing its bearings and implications as a true explanation or description of the facts in a case we must test it carefully for its validity Having found out by a process of deductive reasoning precisely what it implies, we must demonstrate that there is identity between its implications and the actual data that we have accumulated, or can accumulate, regarding the patient If the diagnostic suggestion as developed by ratiocination be found to be out of accord with the facts collectable we dare not give credence to it. Accordance in composition with what has been or can be, observed is the sole real test for the validity of a diagnostic suggestion

If, on looking over our amassed data, we find some single fact that seems to be in absolute conflict with some implication of our reasoned out suggestion, though the other facts are in entire conformity, we shall do well to question the accuracy of our observation on the one hand and the flawlessness of our reasoning on the other If the discordant fact be confirmed by a second observation and if it can be shown that there has been no fallacy in reasoning out the implications of a diagnostic suggestion, the latter, unless it can be so modified as to do away with the discrepancy must be regarded as untenable Any absolute conflict between clinical facts and diagnostic suggestion is fatal to the suggestion as a whole for in the phrase of the logicans, "*falsus in uno falsus in omni*" It must surely be quite clear that what is true of one thing must be true also of its equivalent

In this last or fifth stage of the diagnostic procedure we have to deal, then with the verification or corroboration, of our conjectural ideas It will be recalled that in the third stage of our inquiry we allowed the particular facts that we had accumulated regarding the patient to call forth in our minds suggestions of a general nature that might explain these facts or that might at least classify them under a common head, we there tried by an inductive process to pass from certain results or consequences (our collected data) to some general conceptions from which they might be presumed to flow It will also be remembered that in he fourth stage of our study these suppositional general conceptions were by a process of deduction reasoned out fully as to their bearings and implications through ratiocination we determined what particular clinical facts or consequences ought to be present in the patient if the general ideas were valid Now we come to the last stage of the diagnostic inquiry in which our task consists in com

patient or additions to knowledge that may contribute to the welfare of future generations) will in some degree determine the methods of clinical investigation employed and the scope of the diagnostic inquiry

The natural capacity the experience and the ideals of the diagnostician will have their influence upon the work that he does They will reveal themselves in problem recognition in the practical technique of fact accumulation in creative imagination in reasoning power in verification in philosophic grasp and in esthetic appreciation It is well now and then perhaps to take stock of the personal qualities that make for success in diagnosis What Faraday said of the philosopher is very applicable to the diagnostician of the higher type He 'should be a man willing to listen to every suggestion but determined to judge for himself He should not be biased by appearances have no favorite hypothesis, be of no school and in doctrine have no master He should not be a respecter of persons but of things Truth should be his primary object If to these qualities be added industry he may indeed hope to walk within the veil of the temple of nature

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will indulge in a positive decision and advance in a wrong direction. The only safe way to arrive at accurate diagnostic conclusions or beliefs is to follow the slow process that has been indicated, namely, fact accumulation by observation and experiment lying with the facts that tentative ideas of solution may be engendered reasoning these out fully as to their implications comparing these implications with the facts to see whether or not identity can be established, if necessary making further observations or experiments to extend the facts and testing one suggestion after another until at least some one of them can be corroborated and accepted as valid, then and not until then should a diagnostician permit himself to feel that his problem has been solved

The best diagnostic brain fortified by a large experience, will sometimes make mistakes in diagnosis even when all the precautions that have been referred to have been observed Indeed it has been among the highest type of clinicians from the earliest times on, that can be found most often the evidences of willingness to acknowledge that " experience is fallacious and judgment difficult." No medical man is so expert or so careful that he never arrives at diagnostic conclusions that later on, have to be revised Exploratory operations on the living and complete autopsies upon fatal cases are most salutary correctives of diagnostic jauntiness The diagnostician who follows his patients to the operating room or their bodies should they die to the morgue learns lessons in modesty and takes the best course for the avoidance of presumption on the one hand and undue diffidence on the other The physician who conscientiously applies the method of science to clinical diagnosis who recognizes how difficult diagnosis in a given case may be, who tries to make accurate observations himself who is willing sometimes to enlist the aid of expert observers in special domains in the collection of data who deduces fully the consequences that flow from any diagnostic suggestions that occur to him, and who insists upon accordance between these reasoned consequences and the clinical facts before he permits himself to arrive at a diagnostic conclusion can feel sure that he is working in the right way and can know that as he grows in knowledge and experience, he will become an ever more expert diagnostician

The extent to which a diagnostic study is carried will depend partly upon the purpose for which the study is made and partly upon the natural endowment and the experience of the man making it The purpose of the general practitioner varies somewhat from that of the consulting physician and the purpose of the latter is different to a certain extent from that of the man who devotes his life to original investigation The particular aim that the diagnostician has in view (welfare of the single

CHAPTER XVI

TESTS OF FUNCTION IN INTERNAL MEDICINE

By HENRY A CHRISTIAN

Table of Contents

Introduction

When body structures function within the limits of what is considered normal variation and when the function of each structure is correlated with that of all the other structures in the body so that these structures are coordinated in their activities to produce an harmonious total activity we consider the result to be what we term health In contrast dysfunction of any structure or structures of the body not compensated by that of other structures results in what we term sickness or disease Such dysfunctions of body structures are of primal importance in clinical internal medicine or the study of medical patients who have the symptoms or signs of sickness or disease

Body dysfunctions as referred to in the preceding paragraph express themselves in symptoms and signs of sickness or disease and their recognition and evaluation are necessary to diagnosis and treatment For an adequate understanding and evaluation of such symptoms and signs knowledge of the function of the various body structures is needed so that the internist may know which are and which are not functioning within normal limits as determined from the accumulated recordings of many studies Many methods for such studies or as we term them tests of function have been developed and applied to human beings both well and sick Repetition has determined for each test what we regard as the limits of normality In drawing conclusions for the individual it needs to be recognized that one form of decrease in function often can and is

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Determination	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Ascorbic acid (vitamin C)	Plasma	0.5	0.4–1.0 mg per 100 cc (fasting)	Butler, Cushman and MacLachlan, *J Biol Chem* 150 453 1943
Ascorbic acid	White cells	8 (whole blood)	25–40 mg per 100 cc	*Ibid*
Bilirubin (van den Bergh test)	Serum	2	Direct 0.4 mg per 100 cc indirect (total) 0.7 mg per 100 cc	Malloy and Evelyn, *J Biol Chem* 119 481 1937
Calcium	Serum	2	9.0–10.5 mg per 100 cc	Fiske and Logan, *J Biol Chem* 93 211 1931 Folin, *Lab Manual Biol Chem* 5th ed p 351
Carbon dioxide (content)	Serum	0.5	26–28 meq per liter	Van Slyke and Neill, *J Biol Chem* 61 523 1924 Peters and Van Slyke, *Quant Clin Chem* Vol II (Method) p 283
Carotenoids (total)	Serum	2	100–300 int units per 100 cc	Josephs, *Bull Johns Hopkins Hosp* 65 112 1939 (modified for photocolorimeter and calibrated with haliver oil of specified vitamin A content)
Vitamin A	Serum	2	40–160 int units per 100 cc	
Chloride	Serum	0.5	100–106 meq per liter	Wilson and Ball, *J Biol Chem* 79 221 1928
Cholesterol	Serum	0.5	1[illegible]0–230 mg per 100 cc	Bloor, *J Biol Chem* 24 227 1916
Cholesterol esters	Serum	0.5	65 per cent of total cholesterol	Bloor and Knudson, *J Biol Chem* 27 107 1916
Glucose	Blood	0.1	70–100 mg per 100 cc (fasting)	Folin, *Lab Manual Biol Chem* 5th ed p 307 Folin, *New Eng J Med* 206 727 1932

compensated for by an increased functional activity of some other body structure so that not one but several tests of function are needed to evaluate what seem to be departures from normal limits of function affecting significantly the individual

In the period of early editions of Oxford Medicine many tests of function were so new that they had not been incorporated in readily available descriptions of many diseases Consequently it seemed desirable to describe in some detail in one place numerous tests of function which had been recognized as useful in the examination of individual patients Their use then constituted something new in internal medicine, the results obtained from them were yielding important data not otherwise readily attainable, applicable to diagnosis and treatment At present tests of function have become so generally used and the figures and other data obtained from them so well known that no longer is a separate consideration of them needed Descriptions of many tests of function and their interpretation now are incorporated in the chapters in Oxford Medicine on different diseases Also there are available excellent books on diagnosis and diagnostic technics where descriptions of tests of function and their interpretation will be found The reader, seeking information about different tests of function is referred to other chapters in Oxford Medicine and to the books just cited There he will find tests of the function of almost every structure in the body described and interpreted with advice as to which tests to use and when

It has seemed worth while however, to record in this chapter a considerable number of the normals for various laboratory tests many of which are needed for an appreciation of departures from normal encountered and noted in various places in the chapters in Oxford Medicine Such a table follows

TABLE OF NORMAL LABORATORY VALUES*

BLOOD PLASMA OR SERUM VALUES

DETERMINATION	MATERIAL ANALYZED	MINIMUM QUANTITY REQUIRED cc	NORMAL VALUE	METHOD
Amino acids (CO_2 of carboxyl carbon)	Plasma	2	3 4–5 5 mg per 100 cc	Hamilton and Van Slyke *J Biol Chem* 150 231 1943
Amylase	Serum	2	15–35 units per 100 cc	Adapted from Somogyi *Biol Chem* 125 399 1938

* From Case Records of the Massachusetts General Hospital *New England Journal of Medicine* Vol 234 pages 24–28 1946

Determination	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Phosphorus inorganic	Serum	0 2	3 0–4 5 mg per 100 cc	Fiske and Subbarow *J Biol Chem* 66 375 1925 Folin *Lab Manual Biol Chem* 5th ed p 341 (modified for photocolorimeter)
Potassium	Serum	3–4	3 5–5 0 meq per liter	Fiske and Litarczek in Folin *Lab Manual Biol Chem* 5th ed p 353
Protein Total	Serum	0 5(macro) 0 05(micro)	6 5 8 0 gm per 100 cc	Macro Peters and Van Slyke *Quant Clin Chem* Vol II (Methods) p 691 Micro Lowry and Hastings *J Biol Chem* 143 257 1942
Albumin	Serum	0 5	4 5–5 5 gm per 100 cc	*Ibid*
Globulin	Serum	0 5	1 5–3 0 gm per 100 cc	*Ibid*
Prothrombin clotting time	Plasma	0 3	By control	Quick *J A M A* 110 1658 1938
Pyruvic acid	Blood	2	0 7–1 2 mg per 100 cc (fasting)	Friedemann and Haugen *J Biol Chem* 147 415 1943 Bueding and Wortis *Ibid* 133 585 1940
Sodium	Serum	0 5	136–145 meq per liter	Butler and Tuthill *J Biol Chem* 93 171 1931
Urea nitrogen	Serum	1	10–28 mg per 100 cc	Van Slyke *J Biol Chem* 73 695 1927 Peters and Van Slyke *Quant Clin Chem* Vol II (Methods) p 372
Uric acid	Serum	1	3–5 mg per 100 cc	Folin *J Biol Chem* 101 111 1933

The value parallels the rate of growth diminishing from approximately 14 units per 100 cc in infancy to 5 units in adolescence and thereafter being maintained at approximately 3 5 units

Determination	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Hemoglobin	Blood	0 05	14-16 gm per 100 cc	Evelyn *J Biol Chem* 115 63 1936
Iodine protein bound (thyroid hormone)	Serum	4	4-8 microgm per 100 cc	Talbot Butler Saltzman and Rodriguez *J Biol Chem* 153 479 1944
Magnesium	Serum		1-2 meq per liter	Briggs *J Biol Chem* 59 255 1924
Nonprotein nitrogen	Serum	0 5	15-35 mg per 100 cc	Folin *Lab Manual Biol Chem* 5th ed p 265
Oxygen Capacity	Blood	3	19-22 vol per cent	Van Slyke and Neill *J Biol Chem* 61 523 1924 Peters and Van Slyke *Quant Clin Chem* Vol II (Method) p 321
Arterial content	Blood	3	18-21 vol per cent	*Ibid*
Arterial percentage saturation	—		94-96 per cent	(Arterial content x 100) ÷ capacity
Venous content	Blood		10-16 vol per cent	*Ibid*
Venous percentage saturation	—		60-85 per cent	(Venous content X 100) ÷ capacity
pH (reaction)	Serum	0 2	7 35-7 45	Hastings and Sendroy *J Biol Chem* 61 695 1924 Peters and Van Slyke *Quant Clin Chem* Vol II (Method) p 96
Phosphatase acid	Serum	1	0 5-2 0 units per 100 cc	Gutman and Gutman *J Biol Chem* 136 201 1940
Phosphatase alkaline	Serum	0 5	2 0-4 5 units per 100 cc	Bodansky *J Biol Chem* 101 93 1933 (using the method for determining inorganic phosphorus)

In the newborn infant values may be as high as 6 mg per 100 cc which then diminish during the first year in childhood they approach the normal adult average value of 3 5 mg

Determination	Minimum Quantity Required cc	Normal Value	Method
Osazone differentiation of	5	0	*Ibid* p 50
Urobilinogen	10	Dilution of 1 4 to 1 30	Wallace and Diamond *Arch Int Med* 35 698 1925
17 ketosteroids	12 hour	Under 8 yr 0–2 mg per 24 hr adolescents 2–20 mg per 24 hr males 8–20 mg per 24 hr females 5 14 mg per 24 hr	Talbot Butler MacLachlan and Jones *J Biol Chem* 136 365 1940 Fraser Forbes Albright Sulkowitch and Reifenstein *J Clin Endocrinol* 1 234 1941

Liver Function Tests

Determination	Amount Administered	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Bromsulfalein	2 mg per kg intravenously	Serum (30 min after injection)	2	Less than 5 per cent retention	Rosenthal and White *J A M A* 84 1112 1925 Peters and Van Slyke *Quant Clin Chem* Vol II (Methods) p 910
Bromsulfalein	5 mg per kg intravenously	Serum (45 min after injection)	2	Less than 5 per cent retention	*Ibid* (modified result ÷ 2 5)
Cephalin flocculation	0	Serum	0 2	Up to ++ in 48 hr	Hanger *J Clin Investigation* 18 261 1939
Galactose tolerance	0 5 gm per kg intravenously	Blood	1	Less than 5 mg at 75 min	Bassett Althausen and Coltrin *Am J Digest Dis & Nutrition* 8 432 1941

The 2 mg method is used in patients with slight jaundice and the 5 mg method in patients without jaundice the method is valueless in patients with obvious jaundice

URINE VALUES

DETERMINATION	MINIMUM QUANTITY REQUIRED cc	NORMAL VALUE	METHOD
Albumin (quantitative)	10	0	Folin *Lab Manual Biol Chem* 5th ed p 225
Creatine	24 hour sample	Less than 100 mg per 4 hr	Folin *Lab Manual Biol Chem* 5th ed p 163
Creatinine	24 hour sample	15–25 mg per kg †	*Ibid* p 159 (modified for photocolorimeter)
Diastase	2	Dilution of 1:4 to 1:16	Stitt *Pract Bact Hæm & Parasitol* 9th ed p 31
Follicle stimulating hormone	24 hour sample	Before puberty less than 6.5 mouse units per 24 hr after puberty 6.5–52 mouse units per 24 hr after menopause 104–600 mouse units per 24 hr	Klinefelter Albright and Griswold *J Clin Endocrinol* 3 529 1943
Sugar			
Total (quantitative)	5	0	Benedict *J A M A* 57 1193 1911
Total (roughly quantitative)	0.5	0	Somogyi *J Lab Clin Med* 26 1220 1941
Fermentable	1	0	Hawk and Bergeim *Pract Physiol Chem* 10th ed p 750
Fructose	1	0	*Ibid* p 772
Galactose or lactose	5	0	(Total sugar × 1.24) minus fermentable sugar

Per kilogram of body weight the excretion is higher in women and children than in men and still higher in infants

† The value depends on the ratio of muscle to fat in the body mass of the patient The higher the ratio the greater the creatinine excretion per kilogram of total body weight Because this ratio is low in infants the excretion per kilogram is low

Hematologic Values

Determination	Minimum Quantity Required cc	Normal Value	Method
Bleeding time	—	*1 to 4½ min*	Lee and White in *Todd and Sanford Clin Diag by Lab Methods* 10th ed p 193
Clotting time	10	8 to 20 min	Duke *J A M A* 55 1185 1910
Sedimentation rate (two methods)	4	Less than 0 35 mm per min	Rourke and Ernstene *J Clin Investigation* 8 545 1930
	4	Less than 15 mm per hr	Modification of Wintrobe and Landsberg *Am J M Sc* 189 102 1935
Hematocrit reading (percentage volume of packed red cells)	2	Male 40–54 per cent female 37 47 per cent	*Ibid*
Hemoglobin	0 05	14–16 gm per 100 cc.	Evelyn *J Biol Chem* 115 63 1936
Mean corpuscular volume	—	80–94 cu microns	(Hematocrit × 10) ÷ red cell (in millions)
Mean corpuscular hemoglobin	—	27–32 micromicrogm	(Gm of hemoglobin × 10) ÷ red cell (in millions)
Mean corpuscular hemoglobin concentration	—	33–38 per cent	(Gm of hemoglobin × 100) ÷ hematocrit

Internal diameter of tube should be 4 mm instead of 2 5 mm

Spinal Fluid Values

Determination	Minimum Quantity Required cc	Normal Value	Method
Initial pressure	—	*70–180 mm of water*	
Cell count	0 2	0–5 mononuclear cells (lymphocytes)	

Determination	Amount Administered	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Hippuric acid	1 77 gm sodium benzoate intravenously	Urine	1 hr sample	Greater than 1 gm	Quick Ottenstein and Weltchek *Proc Soc Exper Biol & Med* 38 7, 1938 Moser Rosenak and Hasterlik *Am J Digest Dis & Nutrition* 9 183 1942

Renal Function Tests

Determination	Amount Administered	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Phenolsulfonphthalein	1 cc intravenously	Urine	Total output	25 per cent or more in first 15 min 40 per cent or more in 30 min 55 per cent or more in 2 hr	Chapman *New Eng J Med* 214 16 1936
Urea clearance	0	Blood and urine	Blood 1 cc urine two 1 hr samples	75 to 125 per cent of normal	Peters and Van Slyke *Quant Clin Chem* Vol II (Methods) p 564

CHAPTER XVII

THE TREATMENT OF DISEASE

By SIR WILLIAM OSLER

I

As true today as when Celsus made the remark The dominant view of the nature of disease controls its treatment As is our pathology so is our practice what the pathologist thinks today the physician does tomorrow Roughly grouped there have been three great conceptions of the nature and treatment of disease

A For long centuries it was believed to be the direct outcome of sin "flagellum Dei pro peccatis mundi to use Cotton Mather s phrase and the treatment was simple—a readju tment in some way of man s relation with the invisible powers malign or benign which had inflicted the scourge From the thrall of this sin and sickness view man has escaped so far as no longer at least in Anglo-Saxon communities to have a proper saint for each infirmity Against this strong bias towards the supernatural even the wisdom of Solomon could not prevail was not the great book of his writings which contained medicine for all manner of diseases and lay open for the people to read as they came into the temple removed by Hezekiah lest out of confidence in remedies they should neglect their duty in calling and relying upon God? And the modern book of reason which lies open to all is read only by a few in the more civilized countries The vast majority are happy in the childlike faith of the childhood of the world I am told that annually more people seek help at the shrine of St. Anne de Beaupre in the Province of Quebec than at all the hospitals of the Dominion of Canada How touching at Rome to see the simple trust of the poor in some popular Madonna such as the Madonna del Parto! It lends a glow to the cold and repellent formalism of the churches In all matters relating to disease credulity remains a permanent fact uninfluenced by civilization or education

B From Hippocrates to Hunter the treatment of disease was one long traffic in hypotheses variants at different periods of the doctrine of the four humors as dominated by some strong mind in active revolt

Determination	Minimum Quantity Required cc	Normal Value	Method
Chloride	2	120–130 meq per liter	Wilson and Ball *J Biol Chem* 79 221 1928
Protein	0 6	15–45 mg per 100 cc	Ayer Dailey and Fremont Smith *Arch Neurol & Psychiat* 26 1038 1931
Glucose	1	50–75 mg per 100 cc	Same as that for blood (see above)
Colloidal gold	0 1	0000000000	Wuth and Faupel *Bull Johns Hopkins Hosp* 40 297 1927

Miscellaneous Values

Determination	Material Analyzed	Minimum Quantity Required cc	Normal Value	Method
Stool fat		Representative sample	Less than 30 per cent dry wt	Tidwell and Holt *J Biol Chem* 112 605 1936
Calculi		Representative sample		McIntosh and Salter *J Clin Investigation* 21 751 1942
Congo red test	Serum		More than 60 per cent retention in serum after 1 hr	Bennhold *Deutsches Arch f klin Med* 142 32 1923

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tical results for example have been the new views on tuberculosis! Not that the discovery of the bacillus itself modified immediately our treatment of the disease but as so often happens a combination of circumstances was responsible for the happy revolution—the recognition of the widespread prevalence of the infection the great frequency with which healed lesions were found and the knowledge of the importance of the character of the tissue soil led to the substitution of the open air and dietetic treatment for the nauseous mixtures with which our patients were formerly drenched We scarcely appreciate the radical change which has occurred in our views even within a few years Contrast with a recent work on tuberculosis one published thirty five or forty years ago In the latter the drug treatment takes up the larger share while in the former it is reduced to a page or two And it is not only in the acute infections that the use of the non naturals as the old writers called them has replaced other forms of treatment but in diet exercise massage and hydrotherapy we are every day finding out the enormous importance of measures which too often have been used with greatest skill by those outside or on the edge of the profession

Thirdly the study of morbid anatomy combined with careful clinical observations has taught us to recognize our limitations and to accept the fact that a disease itself may be incurable and that the best we can do is to relieve symptoms and to make the patient comfortable The relation of the profession to this group particularly to certain chronic maladies of the nervous system is a very delicate one It is a hard matter and really not often necessary (since Nature usually does it quietly and in good time), to tell a patient that he is past all hope As Sir Thomas Browne says 'It is the hardest stone you can throw at a man to tell him that he is at the end of his tether and yet put in the right way to an intelligent man it is not always cruel Let us remember that we are the teachers not the servants of our patients and we should be ready to make personal sacrifices in the cause of truth and of loyalty to the profession Our inconsistent attitude is as a rule the outcome of the circumstances that of the three factors in practice heart head and pocket to our credit be it said the first named is most potent How often does the consultant find the attending physician resentful or aggrieved when told the honest truth that there is nothing further to be done for the cure of his patient! To accept a great group of maladies against which we have never had and can scarcely ever hope to have curative measures makes some men as sensitive as though we were ourselves responsible for their existence These very cases are rocks of offense' to many good fellows whose moral decline dates from the rash promise to cure We work by wit and not by witchcraft and while

it would undergo temporary alteration The peccant humors were removed by purging, bleeding, or sweating and until the early years of the nineteenth century there was very little change in the details To a very definite but entirely erroneous pathology was added a treatment most rational in every respect had the pathology been correct! The practice of the early part of the last century differed very little from that which prevailed in the days of Sydenham except perhaps that our grandfathers were if possible more ardent believers in the lancet

C In the past fifty years our conception of the nature of disease has been revolutionized and with a recognition that its ultimate processes whether produced by external agents or the result of modifications in the normal metabolism are chemico physical we have reached a standpoint from which to approach the problems of prevention and cure in a rational way Let me indicate briefly the directions in which the new science has transformed the old art

In the first place the discovery of the cause of many of the great scourges has changed not only its whole aspect, but indeed we may say the very outlook of humanity No longer is our highest aim to cure but to prevent disease, and in its career of usefulness the profession has never before had a triumph such as we have witnessed in the abolition of many fearful scourges Great as have been the Listerian victories in surgery, they are but guerrilla skirmishes so to speak in *comparison with the Napoleonic campaigns which medicine is waging* against the acute infections These are glorious days for the race Nothing has been seen like it on this old earth since the destroying angel stayed his hand on the threshing floor of Araunah the Jebusite For seventeen years Cuba once a pest house of the tropics has been free from a scourge which has left an indelible mark in the history of the Englishman Spaniard and American of the New World Today the Canal Zone of Panama for years the graveyard of the white man has a death rate as low as that in any city of the United States In the island of Porto Rico, where many thousands have died annually of tropical anemia the death rate has been cut in half by the work of Ashford and others But above all the problem of life in the tropics for the white man has been solved since malaria may now be prevented by very simple measures These are some of the recent results of laboratory studies which have placed in our hands a power for good never before wielded by man

Secondly, a fuller knowledge of etiology has led to a return to methods which have for their object not so much the combating of the disease germ or of its products as the rendering of conditions in the body unfavorable for its propagation and action How fruitful in prac

properly whom the first origin of the cause has not deceived We are still far from the goal in some of the most important and fatal infections but anyone acquainted in even slight measure with the progress of the past twenty years cannot but have confidence in the future Considering that the generation is still active which opened the whole question we cannot but feel hopeful in spite of disappointments here and failures there But in our pride of progress let us remember cancer and pneumonia The history of the latter disease affords a good illustration of the truth of the remark of Celsus with which I began Year by year the lesson of pneumonia is a lesson of humility For purposes of comparison statistics are not available but it is not likely that the great masters from Galen to Grisolle lost a larger number of cases than we do Pneumonia has always been as today a dreaded and a fatal disease *For one thing let us be thankful We have had the courage to* abandon the expectorant mixtures the depressants the cardiac sedatives the blisters the emetics the resulsives the purges the poultices and to a great extent the bleedings Surely our forefathers must have killed some patients by the appalling ferocity of their treatment or to have stood it the constitutions of those days must have been more robust We still await but await in hope the work that will remove the reproach of the mortality bills in this disease I say reproach because we really feel it and yet act justly for who made us responsible for its benign or malignant nature? We can relieve symptoms but we must find the means which will on the one hand limit the extension of the process loosen the exudate minimize the fluxion control the alveolar diapedesis and on the other hand diminish the output of the toxins neutralize those in circulation or strengthen the opsonic power of the blood But some one will say Is this all your science has to tell us? Is this the outcome of decades of good clinical work of patient study of the disease of anxious trial in such good faith of so many drugs? Give us back the childlike trust of the fathers in antimony and in the lancet rather than this cold nihilism Not at all! Let us accept the truth however unpleasant it may be and with the death rate staring us in the face let us not be deceived with vain fancies Not alone in pneumonia but in the treatment of certain other diseases do we need a stern iconoclastic spirit which leads not to nihilism but to an active skepticism—not the passive skepticism born of despair but the active skepticism born of a knowledge that recognizes its limitations and knows full well that only in this attitude of mind can true progress be made I hope to live to see a true treatment of pneumonia Before long we should be able to cope with the products of the pneumococci, it may indeed come within the list of preventable diseases

these patients have our tenderest care and we must do what is best for the relief of their sufferings we should not bring the art of medicine into disrepute by quack like promises to heal or by wire drawn attempts to cure in what old Burton calls "continuate and inexorable maladies"

Fourthly the new studies on the functions of organs and their perversions have led to most astonishing results in the use of the products of metabolism which time out of mind physicians have employed as medicines Pliny's "Natural History" (Bohn London 1855 57, vol ii, 291) is a storehouse of information on the medicinal use of parts of animals or of various secretions and excretions Much of the humbuggery and quackery inside and outside of the profession has been concerned with the use of the most unsavory of these materials The seventeenth century pharmacopeias were full of them and in his oration at the Hunterian Society 1902, Dr Arthur T Davies has given an interesting historical sketch of their use in practice Modern metabolic therapy represents one of the greatest triumphs of science The demonstration of insufficiency of the thyroid gland is a brilliant example of successful experimental inquiry, and as time has passed the good results of treatment in suitable cases have become more and more evident Before long no doubt, we shall be able to meet, in the same happy way, the perverted functions which lead to such diseases as exophthalmic goitre Addison's disease, and acromegaly, and as our knowledge of the pancreatic function and carbohydrate metabolism becomes more accurate we shall probably be able to place the treatment of diabetes on a sure foundation And it is not only on the organic side hat progress has been made Important discoveries relating to the metabolism of the inorganic constituents such as those relative to acidosis have opened a new and most hopeful chapter in scientific medicine

But the best of human effort is flecked and stained with weakness and even the casual observer may note dark shadows in the bright picture Organotherapy illustrates at once one of the great triumphs of science and the very apotheosis of charlatanry One is almost ashamed to speak in the same breath of the credulousness and cupidity by which even the strong in intellect and the rich in experience have been carried off in a flood of pseudo science This has ever been a difficulty in the profession The art is very apt to outrun or override the science, and play the master where the true role is that of the servant

And lastly we have advanced firmly along a new road in the treatment of diseases due to specific microorganisms with the toxic products of which we are learning to cope successfully The treatment with antitoxins and bacterial vaccines so successfully started bears out the truth of that keen comment of Celsus "He will treat the disease

remarked about Jacob Bigelow that for his professorship of Materia Medica he had very much the same qualifications that a learned unbeliever might have for a professorship of Christian theology No other man of his time had so little faith in drugs I bore this reproach cheerfully coming as I knew it did from men who did not appreciate the difference between the giving of medicines and the treatment of disease moreover it was for the galled jade to wince my withers were unwrung The heavy hands of the great Arabians grow lighter in each generation Though dead Rhazes and Avicenna still speak not only in the Arabic signs which we use but in the combinations and multiplicity of the constituents of too many of our prescriptions We are fortunately getting rid of routine practice in the use of drugs How many of us now prescribe an emetic? And yet that shrewd old man Nathanial Chapman who graced the profession of Philadelphia for so long used to say Everything else I have written may disappear but my chapter on emetics will last! How much less now does habit control our practice in the use of expectorants? The blind faith which some men have in medicines illustrates too often the greatest of all human capacities—the capacity for self deception One special advantage of the skeptical attitude of mind is that a man is never vexed to find that after all he has been in the wrong It is an old story that a man may practice medicine successfully with a very few drugs Locke had noticed this probably in the hands of his friend Sydenham since he says You cannot imagine how far a little observation carefully made by a man not tied up to the four humors would carry a man in the curing of diseases though very stubborn and dangerous and that with very little and common things and almost no medicine at all Boerhaave commented upon this truth in a remark of Sydenham that a person well skilled in cases seldom needs remedies The study of the action of drugs always beset with difficulties is rapidly passing from the empirical stage and this generation may expect to see the results of studies which have already been most promising It is very important that our young men should get oriented early in this matter of drug treatment Our teachers used to send us to the works of John Forbes (Nature and Art in the Cure of Disease J Churchill London 1857) and to Jacob Bigelow (Nature in Disease Ticknor and Fields Boston 1854) for clear views of the subject A book has been written by Dr Harrington Sainsbury the well known London physician and teacher (Principia Therapeutica E P Dutton & Company New York 1907) which deals with these problems in the same philosophic manner It opens with a delightful dialogue between the pathologist and the physician He lays his finger on the weak point of the pure morbid

II

Along these five lines the modern conception of the nature of disease has radically altered our practice. The personal interest which we take in our fellow creatures is apt to breed a sense of superiority to their failings and we are ready to forget that we ourselves, singularly human illustrate many of the common weaknesses which we condemn in them. In no way is this more striking than in the careless credulity we display in some matters relating to the treatment of disease. Recently the *Times* had an editorial upon a remark of Bernard Shaw that the cleverest man will believe anything he wishes to believe, in spite of all the facts and textbooks in the world. We are at the mercy of our wills much more than of our reason in the formation of our beliefs which we adopt in a lazy, haphazard way without taking much trouble to inquire into their foundation. But I am not going to discuss were I able this Shavian philosophy but it will serve as an introduction to a few remarks on the Nemesis of Faith which in all ages readily overtakes doctors and the public alike. Without trust without confidence, without faith in himself in his tools in his fellowmen no man works successfully or happily. For us however it must never be the blind unquestioning trust of the devotee but the confidence of the inquiring spirit that would prove all things. But it is so much easier to believe than to doubt, for doubt *connotes thinking and the expenditure of energy and often* the disruption of the *status quo*. And then we doctors have always been a simple trusting folk! Did we not believe Galen implicitly for 1 500 years and Hippocrates for more than 2 000? In the matter of treatment the placid faith of the simple believer not the fighting faith of the aggressive doubter has ever been our besetting sin.

In the progress of knowledge each generation has a double labor—to escape from the intellectual thralls of the one from which it has emerged and to forge anew its own fetters. Upon us whose work lay in the last quarter of the nineteenth century fell the great struggle with that many headed monster Polypharmacy—not the true polypharmacy which is the skillful combination of remedies but the giving of many—the practice of at once discharging a heavily loaded prescription at every malady or at every symptom of it. Much has been done and an extraordinary change has come over the profession but it has not been a fight to the finish. Many were lukewarm others found it difficult to speak without giving offense in quarters where on other grounds respect and esteem were due. As an enemy to indiscriminate drugging I have often been branded as a therapeutic *nihilist*. That I should even venture to speak on the subject calls to mind what Professor Peabody of Harvard

used successfully say in six cases of amenorrhea very soon a report appears in a medical journal and a few weeks later this report is sent broadcast with the auriferous leaflets of the firm Some time ago a pamphlet came from X and Company characterized by brazen therapeutic impudence and indicating a supreme indifference to anything that could be called intelligence on the part of the recipients That these firms have the audacity to issue such trash indicates the state of thraldom in which they regard us And I would protest against the usurpation on the part of these men of our function as teachers Why for example should Y and Company write as if they were directors of large genitourinary clinics instead of manufacturing pharmacists? It is none of their business what is the best treatment for gonorrhea—by what possibility could they ever know it and why should their literature pretend to the combined wisdom of Neisser and Guyon? What right have Z and Company to send on a card directions for the treatment of anemia and dyspepsia about which subjects they know as much as an unborn babe and if they stick to their legitimate business about the same opportunity of getting information? For years the profession has been exploited in this way until the evil has become unbearable and we need as active a crusade against pseudo science in the profession as has been waged of late against the use of quack medicines by the public We have been altogether too submissive and have gradually allowed those who should be our willing helpers to dictate terms and to play the role of masters Far too large a section of the treatment of disease is today controlled by the big manufacturing pharmacists who have enslaved us in a plausible pseudo science The remedy is obvious give our students a first hand acquaintance with disease and give them a thorough practical knowledge of the great drugs and we will send out independent clear headed cautious practitioners who will do their own thinking and be no longer at the mercy of a meretricious literature which has sapped our independence

Having confessed some of our weaknesses I may with better grace approach the burning question of the day in the matter of treatment An influenza like outbreak of faith healing seems to have the public of both continents in its grip It is an old story—the oldest indeed in our history—and one in which we have a strong hereditary interest since scientific medicine took its origin in a system of faith healing beside which all our modern attempts are feeble imitations Lincoln s favorite poem beginning We think the same thoughts that our fathers have thought expresses a tendency in the human mind to run in circles Once or twice in each century the serpent entwining the staff of Æsculapius gets restless untwists and in his gambols swallows his tail and

anatomist who thinks of the lesion only, and not enough of the function which even a seriously damaged organ may be able to carry on The book should be in the hands of every practitioner and senior student Some of you may have heard of the lecture room motto of that distinguished pathologist and surgeon and the first systematic writer on morbid anatomy in the United States S D Gross "Principles gentlemen principles! principles!! And it is upon these fundamental aspects that Dr Sainsbury dwells in his most suggestive work which I would like to see adopted as a textbook in every medical school in the land

And we are yet far too credulous and supine in another very important matter Each generation has its therapeutic vagaries the outcome as a rule of attempts to put prematurely into practice theoretical *conceptions of disease As members of a free profession* we are expected to do our own thinking and yet the literature that comes to us daily indicates a thraldom not less dangerous than the polypharmacy from which we are escaping I allude to the specious and seductive pamphlets and reports sent out by the pharmaceutical houses large and small We owe a deep debt to the modern manufacturing pharmacist who has given us pleasant and potent medicines in the place of the nauseous and weak mixtures and such firms as Parke Davis & Company of the United States and Burroughs & Wellcome of England have been pioneers in the science of pharmacology But even the best are not guiltless of exploiting in the profession the products of a pseudo-science Let me specify three items in which I think the manufacturing pharmacists have gone beyond their limit and are trading on the credulity of the profession to the great detriment of the public The length to which organotherapy has extended (not so much on the American side of the water as on the European continent) beyond the legitimate use of certain preparations is a notorious illustration of the ease with which theoretical views place us in a false position Because thyroid extract cures myxedema and adrenalin has a powerful action it *has been taken* almost for granted that the extract of every organ is a specific against the diseases that affect it This forcing of a scientific position is most hurtful and I have known an investigator hesitate to publish results lest they should be misapplied in practice The literature on the subject issued by reputable houses indicates on the one hand the pseudo science upon which a business may be built up and on the other the weak minded state of the profession on whose credulity these firms trade A second most reprehensible feature is the laudatory character of literature describing the preparations which they manufacture Foisted upon an innocent practitioner by a traveling Autolycus the preparation is

acknowledge its potency today as effective among the most civilized people the people with whom education is the most widely spread yet who absorb with wholesale credulity delusions as childish as any that have ever enslaved the mind of man

Having recently had to look over a large literature on the subject of mental healing ancient and modern I have tried to put the matter as succinctly as possible In all ages and in all climes the prayer of faith has saved a certain number of the sick The essentials are first a strong and hopeful belief in a dominant personality who has varied naturally in different countries and in different ages Buddha in India and in Japan where there are cults to match every recent vagary, Æsculapius in ancient Greece and Rome our Saviour and a host of saints in Christian communities, and lastly an ordinary doctor has served the purpose of common humanity very well Faith is the most precious asset in our stock in trade Once lost how long does a doctor keep his *clientèle?* Secondly certain accessories—a shrine a grotto a church a temple a hospital a sanatorium—surroundings that will impress favorably the imagination of the patient Thirdly suggestion in one of its varied forms—whether the negation of disease and pain the simple trust in Christ of the Peculiar People of the sweet reasonableness of the psychotherapeutist But there must be the will-to-believe attitude of mind the mental receptiveness—in a word the *faith* which has made bread pills famous in the history of medicine We must however recognize the limitations of mental healing Potent as is the influence of the mind on the body and many as are the miracle like cures which may be worked all are in functional disorders and we know only too well that nowadays the prayer of faith neither sets a broken thigh nor checks an epidemic of typhoid fever

What should be the attitude of the clergy many of whom have been drawn into the vortex of this movement? I feel it would be very much safer to hand over this problem to us It is not a burden which we should ask a hard working and already overwrought profession to undertake or to share It might be a different matter if it were really a gift of healing in the apostolic sense but we know this was associated with other signs and wonders at present conspicuous by their absence Then think of the possibilities of self deception—of the saintly Edward Irving and the gift of tongues of Monsieur de Paris the French priest and the miracles at his tomb to the truth of which two fine quarto volumes with before and after pictures attest! The less the clergy have to do with the bodily complaints of neurasthenic and hysterical persons the better for their peace of mind and for the reputation of the Cloth As wise old Fuller remarked Circe and Æsculapius were

at once in full circle back upon us come old thoughts and old practices which for a time dominate alike doctors and laity As a profession we took origin in the cult of Æsculapius the gracious son of Apollo whose temples widespread over the Greek and Roman world were at once magnificent shrines and hospitals with which in beauty and extent our modern institutions are not to be compared Amid lovely surroundings chosen for their salubrity connected usually with famous springs, they were the sanatoriums of the ancient world The ritual of the cure is well known and has been beautifully described by Walter H Pater in 'Marius the Epicurean' (Macmillan, New York 1907) Faith in the god suggestion the temple sleep and the interpretation of its dream were the important factors Hygienic and other measures were also used and in the guild of secular physicians which grew up about the temples scientific medicine took its origin No cult resisted so long the progress of Christianity, and so imbued were the people with its value that many of the practices of the temple were carried on into the Christian ritual The temple sleep and the nterpretation of its dreams were continued long into the Middle Ages and indeed have not yet disappeared The popular shrines of the Catholic Church today are in some ways the direct descendants of this Æsculapian cult, and the cures and votive offerings at Lourdes and St Anne are in every way analogous to those of Epidaurus

As I before remarked credulity in matters relating to disease remains a permanent fact in our history uninfluenced by education But let us not be too hard on poor human nature Even Pericles most sensible of men when on his deathbed allowed the women to put an amulet about his neck And which one of us brought up from childhood to invoke the aid of the saints and seek their help—which one of us under these circumstances living today in or near Rome if a dear child were sick unto death would not send for the Santo Bambino the Holy Doll of the Church of Ara Coeli? Has it not been working miracles these four hundred years? The votive offerings of gold and of gems from the happy parents cover it completely, and about it are grateful letters from its patients in all parts of the world No doll so famous no doll so precious! No wonder it goes upon its ministry of healing in a carriage and pair, and with two priests as its companions! Precious perquisite of the race as it has been called with all its dark and terrible record credulity has perhaps the credit balance on its side and in the consolation afforded the pious souls of all ages and of all climes who have let down anchors of faith into the vast sea of superstition We drink it in with our mother s milk and that is indeed an even balanced soul without some tincture We must

complications likely to arise, and he would be taught how to discriminate between the important and the unimportant symptoms of a case This work should form the very basis of his course in medicine and it should be accompanied by a *seminar* to take the place of set lectures in which the features of all the common diseases would be discussed

The hygienic and dietetic management of patients has now come to be such a prominent part of the work of our hospitals that the student may become acquainted with the open air treatment the various modifications of diet suitable to different diseases and the use of massage electricity and other physical agents But too often he is allowed to pick up this information in a haphazard irregular fashion One assistant of the clinic should be detailed to see that every member of the class knows for example how to arrange the open air treatment for a tuberculous patient and how to supervise the diet of a diabetic case The student should prepare personally the various nutritive enemata and be able to give the different kinds of massage and I would have him thoroughly versed in all branches of hydrotherapy A serious difficulty is that nowadays the nurse does a great many things that it is essential the medical student should know how to do—the administration of hypodermics the giving of a cold pack etc

Much more attention should be paid to the important subject of psychotherapy It is not every teacher who has a special gift for this work but if the professor himself does not possess it he should at any rate have sense enough to have an assistant familiar with and interested in the modern methods How many of our graduates have been shown how to carry out a Weir Mitchell treatment or to treat a patient by suggestion? The student should be taught that the very environment of a well managed clinic is in itself an important factor in psychical treatment A Philadelphia friend once jokingly defined my practice at the Johns Hopkins Hospital as a mixture of hope and nux vomica and the grain of truth in this statement lies in the fact that with many hospital patients once we gain their confidence and inspire them with hope the battle is won

And lastly from the day the student enters the hospital until graduation he *should study under skilled supervision* the action of the few great drugs Which are they? I am not going to give away my list A story is told that James Jackson when asked which he considered the greatest drugs replied Opium mercury antimony and Jesuit s bark they were those of my teacher Jacob Holyoke Yes replied his interlocutor and they were those of Holyoke s master James Douglas in the early part of the eighteenth century Mine is a much longer one! The student should follow most carefully the action of

brother and sister, and the wiles of the one are very apt to entrap the wisdom of the other

III

It adds immensely to the interest in life to live in the midst of these problems which concern us so closely We must meet them with an intelligent cheerfulness in the full confidence that the Angel of Bethesda never stirred the waters without happy results It is for us to see that the soldiers we are training for the fight against disease bodily and mental are well equipped for the battle and let me briefly in conclusion indicate how I believe we should teach the art—the management of patients and the cure of disease To know how to deal with disease is the final goal to reach which the whole energies of the student should be directed We all recognize that it is in the out patient departments and in the wards—I wish I could add in the homes of the general practitioners—that he must get this part of his training not in an elaborate course of lectures on the properties and action of drugs In the congested curriculum it is by no means easy to find the proper amount of time for this the most essential part of his education But as we learn the futility of the lecture room as an instrument of teaching men the Art so I think we shall gradually be able to adapt the courses so that plenty of time may be given to the practical study of the treatment of cases under skilled direction We should take over to the hospital of the school the whole subject known in the curriculum as therapeutics The composition of drugs the method of their preparation and the study of their physiological action should be taught in practical classes in the pharmaceutical laboratories In the out patient departments and in the wards much more systematic practical instruction should be given how to treat disease and how to manage patients If we could only get the students for a sufficiently long period in the hospital what helpful courses could be arranged in the senior years! Certain aspects of the subject must be ever kept before the assistants * and the students considered perhaps by different men associated with the clinic according to the special capacity of each one The fundamental law should be ingrained that the starting point of all treatment is in the knowledge of the natural history of a disease Typhoid fever tuberculosis pneumonia and where possible malaria should be used for this important lesson and in the everyday routine observation of cases the student would learn to know the course of the disease its obvious features the

* A post graduate course in medical pedagogy would be most helpful organized by five or six of the large colleges and conducted by them in rotation with teachers selected from the different schools Many able young fellows take years to acquire methods to which they might be introduced in a six months course

CHAPTER XVIII

THE PREVENTION AND CONTROL OF ACUTE RESPIRATORY INFECTIONS

By JOSEPH A CAPPS

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Introduction

Respiratory infections and their prevention have assumed a place of first importance in medicine as a result of the vast epidemics in the World War The medical history of the war will bring out two surprising facts first the rarity of gastrointestinal infections second the frequency of respiratory infections In former wars infections of the alimentary tract such as typhoid and dysentery were responsible for the great epidemics In our military camps of today typhoid and paratyphoid are curiosities and dysentery is an exceptional occurrence The disappearance of this formidable group of diseases can be attributed in part to the general use of typhoid inoculation and in large measure to the safeguarding of the drinking water from contamination During the Spanish American War the danger arising from polluted water was well known but nevertheless careful and comprehensive methods of protection were not carried out Today an army digs its own wells builds reservoirs subjects the water to frequent bacteriological tests and in other ways rigidly and scientifically applies this knowledge No expense is too lavish no effort too great to provide this insurance of soldiers against water borne infections and the results abundantly justify the expenditure The campaign against insect borne diseases has been prosecuted with similar intelligence and diligence The destruction of flies and mosquitoes and their breeding places and the persistent warfare against the body louse has almost rid the army of malaria yellow fever and trench fever

those drugs the pharmacology of which he has worked out in the laboratory He should be sent out from the hospital knowing thoroughly how to administer ether and chloroform He should know how to handle the various preparations of opium * Each ward should have its little case with the various preparations of the ten or twelve great drugs and when the teacher talks about them he should be able to show the preparations He should study with special care the action of digitalis on the circulation in cases of heart disease He should know its literature, from Withering to Cushney It should be taken as the typical drug for the study of the history of therapeutics—the popular phase as illustrated by the old woman who with it cured the Principal of Brasenose, the empirical stage, introduced by Withering in his splendid contribution a model of careful work of which every senior student should know, and the last stage, the scientific study of the drug which he will already have made in the pharmacological laboratory He should day after day personally give a syphilitic baby inunctions of mercury, he should give deep injections of calomel and he should learn the history of the drug from Paracelsus to Fournier He should know everything relating to the iodides and the bromides, and should present definite reports on cases in which he has used them He must know the use of the important purgatives and he should have a thorough acquaintance with all forms of enemata He should know cinchona historically its derivatives chemically and its action practically He should study the action of the nitrites with the blood pressure apparatus and he should over and over again have tested for himself the action, or the absence of action of strychnine, alcohol, and other drugs supposed to have a stimulating action on the heart and blood vessels While I would on the one hand, imbue him with the firmest faith in a few drugs ' the friends he has and their adoption tried,' on the other hand I would encourage him in a keenly skeptical attitude towards the pharmacopeia as a whole ever remembering Benjamin's Franklin's shrewd remark that "he is the best doctor who knows the worthlessness of the most medicines ' You may well say this is a heavy contract and one which it is impossible to carry out Perhaps it is with our present arrangements [1] t + this is the sort of work which the medical student has a right to expect and this is what we shall be able to give him when in his senior years we give up lecturing him to death and when we stop trying to teach him too many subjects

* Sydenham obtained the appellation Opiophilos (Ogle) and the best practitioner is the man who knows best how to use God s own medicine as it has been called

they carried by the droplets of sputum by the expired air by particles of dried sputum in the dust by contact of hands and dishes by food and drink by kissing by drinking cups If the germs can travel by all these routes then it is important to determine the route that is most common in order that our efforts at control may be well balanced

Tuberculosis has been the subject of more intensive study than any other infection Koch s discovery of the tubercle bacillus and the universal prevalence of the disease have been stimuli to a legion of investigators both clinical and experimental It is generally regarded as a respiratory infection but the ordinary chronic cases may well be excluded from the group of acute diseases under discussion The chronicity of tuberculosis the ab ence of any definite incubation period the latency of its lesions and the resistance of the bacillus to destructive influences outside the body all these factors render the study of transmission more difficult than in the acute respiratory infections They likewise greatly complicate preventive measures because any precautions to be effective must be continued over a long period of time Nevertheless there is much to be learned in reviewing the methods and conclusions of the great scientists who for years have endeavored to solve the riddle of the transmission of the bacilli of tuberculosis ([1])

The chief source of infection is the sputum of tuberculous human beings but man may become infected also with bovine bacilli from the meat and milk of tuberculous cows The principal modes of infection that have been championed can here be only summarized

1 The theory of ingestion was advocated by Chauveau and Gerlach who demonstrated that both contaminated meat and milk were capable of infecting man The universal custom of cooking meat almost eliminates this source Further investigations have shown that fifteen to twenty per cent of tuberculosis in childhood are of bovine origin and may be attributed in large part to the use of infected milk

2 The theory of inhalation of dried dust was put forward by Cornet and his associates and was made plausible by the finding of living bacilli in the dust on floors walls and furniture When however it was shown that sunlight destroys even the hardy tubercle bacillus in a state of pulverization this mode of transmission seemed less probable

3 The theory of droplet infection was offered by Flugge who succeeded in infecting animals by direct exposure to the coughing of consumptives Koch endorsed this hypothesis and considered that the tuberculous virus is communicated from phthisical patients to the healthy by means of particles of sputum expelled in coughing

4 The theory of mouth and throat infection combines and includes both the ingestion and inhalation methods It differs from both in that

Contrast these brilliant results with our experience in the management of respiratory infections Influenza measles, pneumonia and streptococcus infections flourish and spread without let or hindrance both in military and civil communities A multitude of precautions are employed and enforced with laxity or strictness according to the individual bias of officials but apparently these diseases are checked only by the exhaustion of susceptible human material

The history of successful control of any infection reveals the important truth that the manner in which the virus gains entrance into the body must be known The causative germ need not be identified in order to work out efficient prevention The attack on yellow fever was most complicated and quite unavailing until it was discovered that the virus entered the body only through the bite of the mosquito After this knowledge was obtained although the germ was still unknown, the methods of prevention became direct simple and effective

Therefore the most intensive study should be directed to definite understanding of the portals of entry and the means of conveyance of the virus of infection in order to insure success in its control or prevention

So called Acute Respiratory Infections

The classification of this group is somewhat arbitrary and provisional and includes the majority of the contagious diseases, namely influenza pneumonia measles whooping cough mumps meningitis diphtheria scarlet fever septic sore throat, acute pulmonary tuberculosis as well as ordinary colds and bronchitis Some of these infections are strictly speaking, not in the respiratory tract Thus mumps affects the ducts leading from the mouth to the salivary glands Septic sore throat affects tonsils and pharynx which form as it were a crossing of the respiratory and digestive highways But it is supposed that these infections are governed by the same laws of transmission as the true respiratory infections and until proof to the contrary is offered they are included It is worthy of note that the specific germs of all these diseases have been identified with the exception of scarlet fever measles influenza and perhaps the ordinary colds and bronchitis

TRANSMISSION OF RESPIRATORY DISEASES

Our notions concerning the transmission of the acute respiratory infections are founded too much on traditional ideas and too little on experimental evidence We are warranted in assuming that the germs pass from the infected to the healthy individual but in what way? Are

they carried by the droplets of sputum by the expired air by particles of dried sputum in the dust by contact of hands and dishes by food and drink, by kissing by drinking cups If the germs can travel by all these routes then it is important to determine the route that is most common in order that our efforts at control may be well balanced

Tuberculosis has been the subject of more intensive study than any other infection Koch's discovery of the tubercle bacillus and the universal prevalence of the disease have been stimuli to a legion of investigators both clinical and experimental It is generally regarded as a respiratory infection but the ordinary chronic cases may well be excluded from the group of acute diseases under discussion The chronicity of tuberculosis the absence of any definite incubation period the latency of its lesions and the resistance of the bacillus to destructive influences outside the body all these factors render the study of transmission more difficult than in the acute respiratory infections They likewise greatly complicate preventive measures because any precautions to be effective must be continued over a long period of time Nevertheless there is much to be learned in reviewing the methods and conclusions of the great scientists who for years have endeavored to solve the riddle of the transmission of the bacilli of tuberculosis (¹)

The chief source of infection is the sputum of tuberculous human beings but man may become infected also with bovine bacilli from the meat and milk of tuberculous cows The principal mode of infection that have been championed can here be only summarized

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it lays great stress on the transmission of sputum to the mouth by the hands eating and drinking utensils etc Also it emphasizes the frequency of primary invasion of the tonsils and throat in distinction to primary invasion of lungs or intestines Krause favors this theory above the others *He believes the spraying experiments of Flügge were not rigidly* controlled since the mouth was sprayed as well as the nose Recently however Rogers (²) has wrapped guinea pigs completely in cloth, includ ing the mouth and subjected them to a spray of finely divided particles of sputum Invariably they contracted pulmonary tuberculosis in a few weeks

From a review of these investigations we may conclude that many persons are infected in childhood through the milk of tuberculous cows, many by means of sputum droplets coughed into the mouth and no e a small number by inhalation of dry contaminated dust an unknown number by means of mouth infection through the medium of contami nated hands and utensils The factors concerned in the transmission of tuberculosis must all receive due consideration in any study of the acute respiratory infections

Sources of Infection in Acute Respiratory Diseases

The infective virus is known to be in the mucous secretions of the mouth throat bronchial tubes or nose in all of the so-called acute respira tory infections namely pneumonia influenza measles mumps strepto-coccus infections diphtheria scarlet fever septic sore throat whooping cough, and the common colds This affords a safe starting point for the study of transmission The blood in a few diseases may also contain the pathogenic germs e g in pneumonia and streptococcus infections but there is no evidence that these infections are ever communicated through the medium of the blood except possibly by invasion of wound Open wounds or mustard gas burns invaded by diphtheria were believed to be an active source of throat diphtheria in hospitals near the front in France but in civil life such occurrences are probably rare Food and drink are also potential dangers but the virus usually reaches them through the medium of infected sputum

It is safe to assume that the ultimate source of infection however transmitted usually lies in the sputum or nasal secretions The portals of entry with few exceptions are the mouth throat nose and perhaps the eyes These assumptions are tenable regardless of the different theories of the modes of communicability

Routes of Transmission

The possible routes of travel of infected mucus from sick to healthy are numerous and much discussion has arisen over their relative importance They may be classed as follows

(1) *The Direct Routes* —(a) Transmission by the spray of mucus droplets from the mouth and nose of the diseased to the healthy during the act of talking coughing and sneezing Flugge (³) found that the expired breath carried no bacteria that talking expelled occasional particles of mucus while sneezing and coughing projected a spray to a distance of 1 meter Doust and Lyon (⁴) recovered bacteria on a Petri dish at a distance of ten feet from the person coughing

(b) Similar transmission of droplets from a carrier to a healthy individual The importance of the carrier as a disseminator of contagion has been more and more emphasized in recent years

(c) Transmission by kissing

(2) *The Indirect Routes* —(a) Inhalation of sputum in the form of dust especially after dry sweeping of floors walks and streets In the southern camps an increase in measles and streptococcus infections was noted following dust storms Most bacteria die rapidly after drying and exposure to sunlight so that this danger may be more apparent than real

(b) Hand to mouth infection The patient coughs in his hand and soils door knobs pens furniture or transmits the mucus to others in hand haking This virus collected on the hands of the healthy reaches the mouth while wetting the fingers or eating and thus gains entrance to the body

(c) The use of contaminated canteens drinking cups and eating utensils According to Lynch and Cummins ( ) the custom of soldiers washing the mess kits in a common can of lukewarm water disseminates infection partly by contaminating the kits but more particularly by transplanting germs from the water to the hands which eventually find their way to the mouth

(d) Use of a common wash basin or bowl In hotels or camps the wash basin is often used for brushing the teeth or washing the mouth thus opening the way for infection of the next person who washes his face in the same receptacle

(e) Exchange of pipes and cigarettes a habit prevalent among soldiers

(f) Food contaminated by diseased individuals and by carriers

(g) Milk has long been recognized as a vehicle for transmission of infectious diseases to man The first organisms found to be carried by milk were those of typhoid dysentery and cholera Later on it was

repeatedly demonstrated that diphtheria scarlet fever and septic sore throat were disseminated by milk During the last decade formidable epidemics of septic sore throat in Boston Baltimore and Chicago have been definitely traced to the milk supply as well as many smaller outbreaks

The contamination of the milk supply with the organisms of diphtheria scarlet fever and septic sore throat occurs in various ways but some of the following conditions are usually associated with milk borne epidemics (a) Cases of active infection or of carriers are found among the milkers (b) Cases of active infection or of carriers exist among the milk handlers (c) Milk vessels bottles containers etc are infected Sometimes the human agent is not discovered, but he may be on the farm at the collecting station or employed as a distributor (d) *Bovine mastitis* resulting from infection with human pathogenic germs is a source that is probably more common than formerly supposed The evidence in favor of scarlet fever germs affecting the udders is discussed by Savage ([6]) Since the causative organism of scarlatina is unknown the question is not capable of proof by experimentation and is supported only by the occurrence of garget and ulcerated teats in certain scarlatina outbreaks Diphtheria bacilli of definite pathogenic character were found by Ashby ([7]) in ulcers on the teats of cows during the investigation of a milk borne epidemic of scarlet fever but no instances of diphtheria mastitis have come to the attention of the writer

Septic streptococcus sore throat has been traced to bovine mastitis Strains of hemolytic streptococci similar to those found in culture from septic sore throat patients have been identified in milk of gargety cows Experiments ([8]) have shown that streptococci of human origin injected by catheter into the udder of a healthy cow will result in mastitis After producing an abrasion of the teat and rubbing in a suspension of human streptococci an ascending infection of the ducts took place finally invading the udder For several weeks thereafter pus cells and streptococci were present in large number in the milk

Theobald Smith and his co workers ([9]) believe that bovine mastitis due to infection with strains of human streptococci may explain the explosive nature of the outbreaks It is probable that in bovine mastitis from human streptococci the ultimate source is the sputum of the milker carried to the cow s teats by contaminated hands Mastitis of this type is a massive infection capable of provoking sudden and extensive outbreaks of sore throat lasting several weeks How frequently epidemics actually spring from this source can be determined only by further investigation

Factors Influencing the Spread of Respiratory Infections

The analysis of the causes that are responsible for the spread of these diseases does not permit of arbitrary and dogmatic conclusions Observers of a given epidemic will frequently place a very different value on the admitted facts of evidence Much is gained by classifying causes into three groups (1) factors concerned with proximity (2) factors concerned with lowered resistance or increased susceptibility (3) other factors

The relative importance of the first two groups depends to a degree not generally appreciated on the nature of the disease in question Thus Zinsser ([10]) points out that susceptibility is almost universal in certain infections e g mumps measles influenza and streptococcus infections Hence in these diseases proximity and contact are the primary etiological elements of the problem and susceptibility plays a secondary role

On the other hand most individuals have a considerable resistance to pneumococcus pneumonia meningitis and scarlet fever even though exposed to these diseases Consequently conditions tending to lower resistance assume the greater importance while proximity is of lesser moment

No pretense is made that causes falling in both groups may not be operative and that often the two may not overlap but the distinction here formulated will be found useful for a better valuation of factors and for more intelligent application of preventive measures

One must remember also that the natural resistance of an individual to a disease such as pneumonia is quite broken down by another antecedent infection such as influenza or measles

(1) *Factors Concerned with Proximity* —These are most important in the diseases to which there is an almost universal susceptibility namely influenza measles streptococcus infection and mumps

(a) *Overcrowding* in civilian life and in the military service is the bane of sanitarians Overcrowding in camps in hospitals at ports of embarkation in barracks and on troop transports was by common consent the overwhelming factor in causing the great prevalence of respiratory diseases in our army In barracks the bunks were close together at the mess tables men sat on opposite sides with only three or four feet intervening in reading and recreation rooms and about the stoves they gathered in compact groups in hospital wards with the regulation provision of fifty beds there was a space of two feet between beds but in wards with seventy to seventy four beds which were the rule in the American Expeditionary Force during the active period only five inches separated the beds On transports the men in crowded sleeping quarters

suffered also from a lack of ventilation and air foul beyond description The opportunities for direct and indirect dissemination were legion

(b) Promiscuous *dissemination of sputum and nasal secretions* incident to crowding This includes the contamination of drinking cups and dishes the conveyance by soiled hands of secretions to cigarettes pipes or directly to the mouth and the use of a common wash bowl All of these details of personal hygiene and cleanliness are rendered difficult or impossible by living in crowded quarters

(2) *Factors Concerned with Lowered Resistance* —(a) Exhausting drills or long marches, (b) exposure to rain and cold (c) inadequate bed covering (d) poor ventilation (e) racial susceptibility, (f) men from rural homes are more susceptible to infectious diseases than those from the city

(3) *Other Factors* —(a) The failure to recognize and isolate early cases of infection exposes others to contagion Many army surgeons were culpable in this respect (b) Failure to discover and isolate carriers of diphtheria bacilli and meningococci

Emerson ([11]) attributes the unfavorable conditions responsible for the high rate of respiratory infections in the American Expeditionary Force partly to inevitable limitations of transportation on land and sea imposed by military operations and requirement of speed in troop movements partly to lack of labor and materials for building shelters partly to lack of discipline in matters of personal hygiene and partly to lack of imagination on the part of medical officers who subordinate the protection of a community to the symptomatic treatment of the patient

The Role of Carriers

In every epidemic there are many mild or atypical cases of infection that are not reported to the health authorities There are also many carriers or healthy individuals who harbor pathogenic germs without being infected Presumably the sick are more liable to infect others than the carriers but the sick are quarantined while carriers are allowed their freedom Thus carriers may become important factors in the spread of disease Failure to control diphtheria and meningitis epidemics has been attributed to the neglect of carriers

Since carriers are often very numerous it is not practicable to attempt universal cultures of a community or camp But cultures of contacts in families wards or small military organizations are desirable since the segregation of carriers has often been the means of ending an epidemic The whole problem of carriers needs further investigation which may lead to radical changes in preventive medicine

The Importance of Cross Infections

In times of peace contagious hospitals have always been embarrassed by cross infections especially of scarlet fever and diphtheria or of measles and diphtheria Frequently these cross infections have been contracted in the hospital But in our military camps the tremendous importance of cross or multiple infections in the respiratory tract has been for the first time brought home to the profession Reports from our home camps indicate that measles uncomplicated was of little danger but that the secondary invasion of streptococci causing pneumonia gave rise to a formidable mortality Similarly in the American Expeditionary Force influenza alone was rarely serious Most clinicians and bacteriologists are of the opinion that the deadly pneumonia following in the wake of influenza was due to a secondary infection of streptococcus pneumococcus or other germs Multiple infections were the rule in fatal cases This so called polybacterialism finds its simplest explanation in promiscuous transfer of infected secretions from one individual to another An initial attack of measles or influenza renders the mouth and air passages highly susceptible to other pathogenic organism Toxic gases likewise prepare the soil for bacterial growth

Cross infections may occur anywhere but there are certain places where the combination of close quarters and the presence of carriers of different organisms is highly favorable Such places are the hospital trains where gas influenza streptococcus pneumococcus and wounded patients are herded together in sitting compartments or placed in adjacent bunks the ambulances and the receiving wards where these men are again brought together with new contacts and finally in the hospital wards We have repeatedly observed the onset of pneumonia within forty eight hours of the arrival of a convoy on these trains In civil life cross infections are favored by the living conditions in charitable institutions college dormitories and public schools The probability that hospitalization is responsible for the dissemination of bacteria is pointed out by Cole (¹) who found that the number of *measles patients that on* admission to a hospital harbored streptococcus hemolyticus was small but that the majority of these patients acquired the organism during their residence in the hospital

Levy and Alexander (¹³) recovered streptococci from the throats of 14 8 per cent of 489 new recruits whereas 95 men in one organization that had been in camp for months yielded 83 per cent positive cultures Still more significant is their observation that most of the clean cases in measles wards acquired streptococci within a week from neighboring streptococcus carriers Bronchopneumonia following measles occurred

exclusively in those patients who were carriers of streptococci. Careful studies of this kind on cross infections in influenza are not available but would probably give similar results. It is not an overstatement to assert that in the great epidemics of influenza and measles in the army and in civil hospitals cross or secondary infections with streptococcus pneumococcus and other organisms ushered in most of the pneumonias and were therefore, responsible for a large percentage of deaths.

PREVENTIVE MEASURES

The campaign against the epidemics of respiratory infections so far has developed very little along offensive lines. It is essentially a series of defensive battles designed to give protection to humans against the bacterial weapons and to minimize the effect of wounds thereby inflicted. The methods of proved value may be considered under the following classification: (1) early recognition of infection, (2) prophylactic vaccination, (3) destruction of pathogenic germs, (4) the aseptic method, (5) blocking transmission by physical means.

(1) *Early Recognition of Infection*.—The immediate discovery and identification of a case of infectious disease is the keynote of success in controlling an epidemic. Prompt isolation and quarantine of the first case during the contagious period is more efficacious in stamping out the disease than the most elaborate general measures later on when the contagion has spread and become intrenched in many foci. Confinement of the patient to bed simplifies quarantine and renders it more effective and at the same time secures to the individual his maximum power of resistance.

(2) *Prophylactic Vaccination*.—Antidiphtheria inoculation by the toxin antitoxin method marks a great advance in the control of diphtheria. The immunizing process requires several weeks and is most advantageously employed among the children of the crowded cities where diphtheria is endemic. Zingher ([14]) advocates its more general use in young children as the best means of eliminating the existing prevalence of the disease. For the immediate protection of individuals exposed to infection the single dose of prophylactic antitoxin affords an immunity lasting several weeks and because of its quick action is the method of choice.

In prophylactic immunization against pneumonia some progress has recently been made. Cecil and Austin ([15]) obtained encouraging results at Camp Upton where 12 519 men were vaccinated with Types I, II and III pneumococcus. During an observation period of ten weeks none of these cases that had received two or more injections developed pneu

monia of these three fixed types whereas in a control of about 20 000 men unvaccinated there were 26 cases of pneumonia of Types I II and III Later Cecil and Vaughan ([18]) u ed a lipovaccine in 13 460 men at Camp Wheeler for the same types of pneumococcus Although consid erable protection was conferred the prevalence of influenza obscured the effects of the pneumococcic immunization and the results were not so favorable as at Upton During measles streptococcus and influenza epi demics Type IV pneumococcus pneumonias are numerous and up to the present time little has been accomplished in preventing this formidable group by vaccination Influenza prophylactic vaccines have been tried with varying success (Rosenow ([17]) McCoy ( ) but the treatment is still in the experimental stage The other respiratory infections have so far proven refractory to immunizing measures

(3) *Destruction of Pathogenic Germs* —The use of antiseptic gargles and sprays has had many advocates Sailer believes that the daily irrigation of the throat in hospital wards causes a marked diminution in cross infections But the disappointing results of these methods in clearing up the throats of carriers of diphtheria bacilli and meningococci have undermined our confidence in their efficacy The removal of dis eased tonsils and adenoids in diphtheria and meningococcus carriers has given excellent results in the experience of Friedberg ([19]) and others and deserves further trial

If the sputum and nasal discharges could be effectively collected on bits of cloth and in sputum cups and burned a definite source of con tagion would be eliminated The enforcement of this precaution in car riers and ambulatory patients is extremely difficult All dishes and drink ing vessels should be sterilized in boiling water Spitting about the wards on the streets and in public conveyances should be rigidly pre vented The danger from fomites in respiratory infections is greatly overrated in the opinion of no less an authority than Chapin ( ) who states that physicians rarely carry disea e from the sick to the well that infection by clothing is rare and that fomites in a room occupied by scarlet fever or smallpox are not likely to convey contagion Upon this general assumption the fumigation of rooms after occupancy by con tagious cases has been limited or abandoned by many of our municipal health departments The belief is strong that most germs die or lose their virulence soon after leaving the body

(4) *The Aseptic Method* —The aseptic method of antisepsie medi cale was introduced by the French for the purpose of combating cross infections in hospitals The method is based on the hypothesis that respiratory infections are transmitted chiefly by contact dissemination by the air being neglected At the Pasteur Hospital in Paris isolation in the

ordinary sense is less emphasized than the aseptic details in the care of the sick. Patients with various contagious diseases are placed in adjoining rooms. The same nurse attends different diseases but observes rigid precautions in wearing a gown that is left in the room and in washing the hands upon leaving the room. Similar methods have been successfully employed in the care of ward patients at the Monsell Hospital in Manchester ([1]) where a sheet covered screen forms a barrier about each bed. The nurse is required to wear rubber gloves whenever a patient is handled and a gown that is always kept inside. Wherever this idea has been put in practice rigidly cross infections have been very few. No one can question the success of the method.

But the conclusion that contact between patients and nurses is the essential and only means of transmission overcome by these precautions seems unwarranted. This technique demands most rigid isolation of patient from patient and the separation of patients by partitions or screens also prevents droplet infection by coughing. From a practical point of view the system is complicated and expensive as a nurse must be highly specialized in the technique by long training before she is competent to take charge of a ward. While freely admitting the efficiency of the aseptic method, we will do well to inquire into ways and means of rendering it more simple and economical at the same time retaining its essential features.

(5) *Blocking Transmission by Physical Means.*—Could it be proved that droplet infection and direct contact were the primary factors in transmission and that indirect contact with sputum, soiled hands and objects were secondary factors, then our attention would be focused on blocking the germs in their course of travel from one person to another. The blocking method is accomplished principally by the following means:

(1) Cubicles or separate rooms. In hospital wards and especially in military hospitals where small rooms are often not available, the sheet cubicle, a sheet suspended on a wire seven feet above the floor and extending from the head to the foot of the bed, has given universal satisfaction.

(2) Face masks. The gauze face mask has long been employed by surgeons in the operating room to prevent droplet infection of wounds. Strong ( ) and his associates worked with impunity among victims of the pneumonic plague in Manchuria by using masks made of gauze reinforced with cotton. Meltzer ([3]) urged the use of a fine net over the faces of patients with infantile paralysis and also over the faces of attendants. To Weaver ([4]) belongs the credit of demonstrating the value of the mask in protecting attendants and physicians from contracting infection. *During a period of eighteen months he succeeded in eliminating* scarlet fever among nurses, whereas in the preceding twenty-one

months eight per cent had acquired the disease At the same time the incidence of diphtheria carriers was reduced from twenty six per cent to about five per cent

Weaver s method afforded such apparent protection to the doctors and nurses at the Base Hospital at Camp Grant that the author ([25]) undertook the experiment of using face masks on patients to protect them against cross infection So long as a patient remains isolated in the cubicle he is protected when he leaves the cubicle he endangers others and is himself exposed to cross infections As a result of numerous cross infections particularly scarlet fever measles and streptococcus we instituted the use of the mask on patients in all wards where respiratory infections were treated Each patient was issued daily a clean mask which when not in use was pinned to his cubicle sheet

Haller and Colwell ([6]) made a careful study of various qualities and thickness of gauze necessary to procure blocking of droplets They advise the use of five layers of gauze with a 32 x 36 mesh when worn by the attendant only and three layers when worn by both attendant and patient The patients were told that the cubicle is like the dugout in a gassed area as long as one remains inside the mask is superfluous but it is dangerous to leave the cubicle unmasked

Since many persons were exposed to both primary and cross infections before reaching the ward the following means were adopted At the regimental infirmary every case with respiratory infection was masked as soon as recognized Upon entering the ambulance every patient sick or well was masked In the receiving ward every ambulatory patient who entered the hospital was masked at the door and all patients continued to wear the mask until they reached the shelter of their ward and cubicles

Before the method of masking patients was introduced and the cubicle alone was employed we had ten instances of cross infection with scarlet fever in wards occupied by other diseases In four instances or forty per cent there were subsequent cases of scarlet fever during the week of quarantine In three wards where measles broke out as a cross infection there was one ward in which a subsequent case of measles developed during the two weeks of quarantine After masks were used universally by patients and attendants the results were as follows in twenty four wards where scarlet fever appeared as a cross infection there was only one ward or five per cent in which a subsequent case developed in twelve wards where measles occurred as a cross infection there were two wards or seventeen per cent in which a subsequent case developed To summarize Before general masking in thirteen wards with cross infection there were five wards or thirty eight per cent with

subsequent cases After masking in thirty six wards with cross infection there were three wards or 8 3 per cent with subsequent cases The statistics in streptococcus cross infections cannot be tabulated because there was no period of quarantine after exposure It may be significant however that only twenty cases of bronchopneumonia developed in over 900 cases of measles although streptococcus infections were prevalent

The Limitation of Isolation Measures

What measure of success can be expected of the isolation methods just described in preventing the spread of epidemics of influenza measles and streptococcus infections in civil communities and in military camps? Can they be depended on to check the onward sweep of these infections? The experience of public health officers and epidemiologists in the army shows very definitely that these barriers cannot withstand the irresistible advance of such epidemics Individuals families organizations may here and there secure protection but the population as a whole is submerged The reason for this failure is that universal enforcement of isolation among healthy people or healthy troops is impossible Even the infected cannot be easily isolated since healthy "carriers" are always numerous and cannot be recognized without taking cultures of all The attempts to rigidly isolate healthy people wherever they congregate in civil life e g compulsory masking as practiced in San Francisco in the recent influenza outbreak would seem doomed to failure as a general measure although doubtless many individuals might thereby secure protection

In army camps where it is possible to quarantine large organizations the chances of success are far greater but in practice they were often disappointing in the case of influenza and measles diseases in which "carriers" cannot be identified because cultures are of no assistance Isolation in meningitis and diphtheria yielded much better results because both sick and "carriers" can be recognized by cultures of the throat The bald truth may as well be faced that in the army influenza measles mumps and streptococcus infections spread rapidly and freely in spite of all the efforts of sanitarians

Isolation Methods in Control of Cross Infections

To stem the tide of a highly contagious disease is one thing to protect healthy individuals from the disease and to protect the sick from cross infections is another In the first situation the individuals are not under personal control and supervision in the second situation the individuals are under the influence of personal discipline Isolation methods are not at all effective in checking the spread of the most contagious diseases and only partly effective in the less contagious ones On the

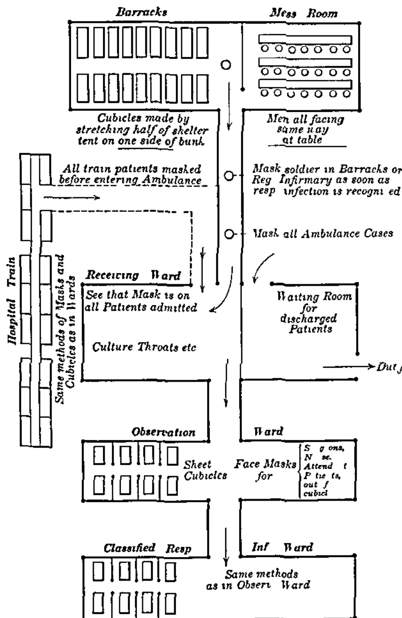


Fig 1—Diagram of the Technic for the Control of Respiratory Cross Infections in Military Camps

other hand isolation is capable of greatly reducing the incidence of cross infections At first blush the control of cross infections appears to be a comparatively insignificant phase of the problem and it is when expressed in mere numbers But its importance defined in terms of mortality is very great for death usually follows in the wake of cross infections

A comprehensive scheme for reducing cross infections in the army is outlined (Fig 1) Most of these measures have been employed in the service but not consistently and rigidly

(1) In camps newly arrived troops should be segregated

(2) In the triage every effort should be made to keep the gas and respiratory infections separated

(3) In hospital trains the patients should be sorted as far as possible to segregate all respiratory infections The proximity of such patients to gassed or wounded soldiers should be avoided Since minor throat and bronchial infections and carriers are a menace the stretcher cases should be separated by a sheet partition The nursing personnel and surgeons should wear masks when on duty

(4) In barracks overcrowding is to be avoided The bunks should be separated by the half of a shelter tent or other partition As soon as a case of respiratory infection is recognized he should be masked and sent to the hospital

(5) In the mess seating soldiers at a narrow table all facing the same direction is a simple and useful expedient for limiting the danger of droplet infection and has been tried with success

(6) All patients traveling by ambulance should be masked

(7) An orderly stationed at the entrance of the receiving ward should see that every patient admitted is masked unless he is suffering from dyspnea The mask should be worn until the patient reaches the shelter of his cubicle Patients awaiting discharge should be kept separate from those awaiting admission

(8) Separate wards are desirable for influenza pneumonia and gassed cases as well as for those diseases ordinarily isolated such as measles and meningitis

The beds should be separated by sheet screens The face masks should be worn by physicians nurses ward men and by all patients when out of their cubicles Within the cubicle the mask may be removed and pinned to the sheet The patient should wear the mask when leaving the cubicle at all times except in the wash room where only one person should enter at a time Meals should be eaten in the cubicle although the patient if masked may be allowed to carry his dishes from and to the kitchen Smoking should be prohibited in these wards as it necessitate removal of the mask and is also harmful to the inflamed air passages

All eating utensils should be sterilized in boiling water after each meal Physicians and attendants after examining or handling a patient should wash the hands with soap and water Masks should be disinfected by soaking an hour in two per cent cresol solution then by boiling half an hour in soap and water In practice the mask may owe much of its value to limiting the opportunities of hand to mouth infection as well as to direct droplet dissemination

Control of Cross Infections in Civil Practice

The principles of prevention are the same in civil as in military practice but their application is quite different owing to the loose organization and lack of discipline in civil communities The immediate diagnosis and reporting of all contagious diseases is a fundamental procedure The reportable diseases should include streptococcus sore throat which is generally neglected by physicians

In carrying out isolation measures in the home emphasis should be laid on the danger of secondary infection to the patient as well as on the spread of the patient s contagion to others Especially in measles and influenza the patient needs this safeguarding so easily afforded by masking the face of nurse and all others entering the sick room and the insistence on cleanliness of hands and eating utensils In this way there is hope of minimizing the frequency of complicating pneumonia otitis media etc

Hospitalization

For years our health departments have believed that the hospitalization of all contagious diseases would bring about a decided diminution of the morbidity rate This has been the motive for building large municipal hospitals for contagious diseases According to Chapin the results of the movement have been disappointing He states that communities in which hospitalization of contagious diseases has been almost complete for years show quite as high prevalence of these diseases as communities in which there is no attempt at hospitalization The bringing together under one roof of many different infections may actually expose the patient to a new disease Moreover the healthy carriers of infection are not controlled by this method In the light of this experience more attention should be given to the supervision of house quarantine not only by city physicians but by visiting nurses capable of instructing the family in preventive measures

Closing of Public Places

During the epidemic of influenza the advisability of closing schools theaters and other places of assembly was heatedly discussed by health officials The danger of contagion was admitted On the other hand it was urged that the discipline, regular hours and good ventilation of the schoolroom afforded less exposure to disease than the uncontrolled mingling of children on the streets The belief is firmly rooted among sanitarians that proximity out of doors where the air is in constant movement is far less liable to disseminate contagion than proximity indoors where the air is often stagnant

For sporadic cases of infectious disease the segregation of the patient and if possible of carriers is sufficient When however an existing epidemic invades a school it is often desirable to close its doors until the force of the infectious wave is spent In theaters and churches much might be accomplished in checking transmission by direct appeal to the audience to always cover the mouth with a handkerchief during coughing and sneezing—a practice introduced by a noted evangelist Teachers in the schools and parents in the home are under obligation to instruct children upon this matter of personal hygiene

Good ventilation of assembly rooms materially lessens the liability of germ dissemination and should receive more attention The air in public libraries schoolrooms and lecture halls where the windows are closed to exclude noise and smoke is often oppressively stale and in consequence favors the spread of contagion

Special Measures

This chapter is intended to treat only of the general principles concerned in the control of respiratory infections since specific therapy will be discussed under the separate diseases Only a few applications of these principles to individual infections need special mention

Pneumonia —The promising work on vaccine prophylaxis has already been referred to Individual isolation of different types of pneumococcus infection in pneumonia wards is advocated by Cole but Zinsser considers this unessential Isolation for the purpose of preventing cross infection with other germs especially streptococcus is, however of undoubted value

Measles is a dangerous disease in proportion to the incidence of secondary infections Hence the importance of isolation measures During the prevalence of streptococcus infections the separation of measles patients harboring streptococci in the throat from the clean cases is deserving of trial Isolation in the home with rigid enforcement of

masking and cleanliness on the part of attendants should diminish the frequency of pulmonary and other complications

Influenza as a primary infection cannot be adequately controlled by isolation or any other measures now known Still it is possible to give a large degree of individual protection to the sick in hospitals by rigid quarantine and by the prevention of secondary infections

Meningitis and Diphtheria demand a search for carriers among contacts by means of throat cultures The isolation of contacts leads to the questionable quarantine of many persons with positive cultures There is need of discretion in avoiding promiscuous culturing of organizations beyond the immediate focus of the disease and also in releasing carriers of non virulent diphtheria bacilli Immunization of contacts yielding a positive Schick test is also a valuable means of restricting the contagion

Streptococcus infections like influenza are at present most difficult of control We must be content to check by isolation methods their invasion of other respiratory diseases Preeminently in limiting secondary streptococcus infections the barriers of cubicle and mask should be efficacious The appearance of a streptococcus outbreak should invariably lead to an investigation of the milk supply Whether the evidence of milk contamination is obtained or not pasteurization or boiling of the milk and milk products is advisable All influences previously discussed that lower the resistance to infection should be avoided as far as possible *but they play a role in cross infections of less importance than* factors of proximity

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CHAPTER XIX

ENVIRONMENT AND ITS RELATION TO HEALTH AND DISEASE

By LLEWELLYS F. BARKER

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From the time of beginning as a fertilized egg-cell to the time of death each human individual is subjected to environmental influences that are ever changing The intra uterine, infantile puerile adolescent mature and senescent periods of life have each of them to a varying degree certain special surroundings that may be of significance both for health and for disease In the formation of environments physical chemical biological psychological and social components participate in greatly differing combinations (Some of these effects are described also in other chapters reference to the index will show where these descriptions may be found)

PHYSICAL COMPONENTS OF ENVIRONMENTS

Among the physical influences of environments are included those of temperature light electricity x rays and radium air pressure and propagated motion

Thermic Influences

These have been of great importance in influencing the development of human civilization as well as of personal hygiene The world man lives in has great

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extremes of temperature, the mean yearly temperature of a climate may be as high as +30° C or as low as −26° C, the mean monthly temperature as high as +39° C or as low as −51° C, and the extreme single temperatures may be as high as +56° C and as low as −63° C, and yet thanks to the heat regulating mechanisms of the body and to the types of clothing and dwellings he has devised, man can continue to exist in such climates for he creates a 'private climate' within the general thermal environment. The mechanisms within man's body for the regulation of his temperature are complex: chemical regulation with heat production depends largely upon (1) muscle contraction (as in shivering) and (2) more rapid combustion processes because of the increased rate of metabolism when the external temperature falls, physical regulation with heat dissipation depends upon the giving off of heat to the surroundings (1) by conduction and radiation and (2) by the evaporation of secreted sweat. These regulatory mechanisms are mediated by vegetative centres in the hypothalamus; afferent impulses to these centres are excited by stimulation of the warm points in the skin by heat and of the cold points by cold, efferent impulses from the same centres pass to the muscles, to the sweat glands and vasomotor apparatus of the skin and to the structures mediating the metabolic rate. Though these heat regulating mechanisms provide excellent physiological methods of defence to changes in the thermal environment, there are limits beyond which they are no longer capable of preventing local or general injury to either heat or cold.

Thus the local injuries ('burns") from excessive heat may vary in degree from erythema and blistering to necrosis and actual charring; if local burns be extensive, symptoms of general intoxication of the body will follow, and death has occurred as the result of a burn of approximately one-eighth of the body surface.

When the human body as a whole becomes overheated, say because of strenuous muscular activity in a very hot environment, so-called "heat stroke" may occur of which several types have been observed, including (1) heat prostration, (2) hyperpyretic heat stroke and (3) forms with gastro-intestinal or psychic symptoms predominant. In the Great War there were many cases among the troops in Mesopotamia and other hot regions with a relatively high mortality. But even in temperate climates heat stroke is frequently met with sometimes in 'epidemics' as in New York City in August 1896.

In "heat stroke' the blood of the body as a whole becomes overheated and causes overheating of the brain centres, in "sun stroke" the same centres may become overheated through the direct over heating of the head.

Excessive cold can cause local injury manifested as "frost bite" or "freezing", there may be every degree of injury from erythema to gangrene. During the World War there were many cases of so-called 'trench foot', following exposure of the feet to melting snow in the trenches. It was found this snow

water withdrew more heat from the feet than dry cold snow did A milder form of local injury following exposure of predisposed persons to cold in our climate is that known as chilblains here however the local tissue disposition is the most important factor cold acting as a provocative cause

The general effects of low temperatures upon the body have been studied both in man and in experimental animals In insufficiently protected persons exposed to cold winds cold water, or snow storms over too long a period the temperature of the interior of the body may fall to so low a level that death results Drunken men Alpine tourists and shipwrecked sailors sometimes meet with death from cold After the preliminary chilling they are overpowered by a sense of fatigue begin to yawn become drowsy and enter into coma

Of late years much attention has been given to the common cold and to the nasal pharyngeal and pulmonary sequels of catching cold Both laymen and physicians are convinced that exposure to cold and damp may be an important etiological factor in catching cold though disposition (inherited or acquired) to colds seems to be just as important and at least in many cases infection also plays a part The effect of the cold may directly injure local tissues many however, are wedded to the hypothesis that the cold through reflex action changes the blood supply of certain organs (nose throat lungs) in which the disease develops Much progress has been made in lessening the susceptibility to colds through wiser methods of clothing better ventilation of hou e practice of out door sports and so called hardening measures Treatment of local infections of the nose mouth throat and paranasal sinuses seems also to be helpful in lessening disposition to catching cold Many persons have found by experience that when after exposure to cold they have observed the premonitory symptoms of a cold they can often abort it by provoking sweat and keeping warm afterwards

Influence of Light

Sunlight if allowed to act upon the skin may cause erythema and dermatitis The erythema produced may occur at once or shortly after exposure and disappear again in a few hours this type is like any burn due simply to the heat action of the light rays and the ultra red rays Another type of erythema the so called photochemical exanthem appears only after a latent period of several hours and is due to the action of the ultraviolet rays this type is often met with among tourists in the high mountains and upon glaciers since the sunlight at high altitudes is said to contain relatively more ultraviolet rays than the light at lower levels The pigmentation that follows the dermatitis is an especial protection against the skin harming effects of ultraviolet rays It is said that the application of a 5 per cent quinine paste to the exposed parts of

the skin when making a mountain or glacier tour, will protect from injury to the skin since this paste will absorb most of the ultraviolet rays

Electrical Influences

About electrical influences in the environment aside from lightning stroke and accidental contact with strong electrical currents but little is known. Death due to being struck by lightning has decreased in houses, since lightning rods have been in use but there has been but little if any change in the number struck in the open. Some five hundred persons yearly die from this cause in the United States.

With the great increase in the use of electricity in industrial establishments and in households, accidental contacts with powerful electric currents have become ever more common so that now approximately ten persons per million of population are killed by such contacts each year in the United States. The majority of these accidents though not all, have been due to contact with alternating currents. In case of contact a person standing in rooms with dry floors carpets or linoleum is safer than one standing in rooms with tiled, brick or cement floors. Many safety devices have been introduced that lessen the likelihood of electrical injury.

When a strong current enters the human body violent muscular contractions occur. It is fortunate when such contractions remove the part, at which the current has entered from contact with the conductor of the current. Sometimes, when the part entered is the hand there is tetanic contraction of the muscles so that the conductor is firmly gripped and cannot be let go. On lightning stroke, the person struck may fall dead, or apparently dead, or he may cry out before losing consciousness.

When the current has not been too strong death does not occur, even comatose patients may be revived especially with artificial respiration. On recovery, evidences of the site of entry and of exit of the current may be seen on the skin (burns, epidermolysis localized œdema ' lightning figures ', necroses). Some patients after injury become hysterical or show other evidences of traumatic neurosis. Occasionally there are sequels in the form of neuritis or of focal lesions within the central nervous system.

Influences of X Rays and Radium

Roentgen rays and the gamma rays of radium have great capacity for penetrating the body because of their extremely short wave lengths. The tissues of the body vary in their sensibility to the action of the rays the lymphadenoid tissues and the gonadal tissues being perhaps most sensitive, the connective

tissues cartilage and bone least sensitive Mild exposures not too often repeated, appear to be harmless whereas stronger and frequent exposures can cause severe damage even death of tissue cells

Because of the sensitiveness of the skin radiologists are careful in examining patients and especially when treating them with larger dosage to avoid the production of a dermatitis hence at any one treatment a single area receives only a certain fraction of a 'skin-erythema dose Chronic dermatitis with hyperkeratoses and changes in the finger nails frequently develops among x ray operators and should be avoided by better protective measures than those formerly used all too many of our pioneer roentgenologists have succumbed to carcinomatous processes that developed upon the basis of skin injuries due to the x rays

With the increased use of radium and of x rays for the treatment of leukæmias hyperthyroidism and neoplasms physicians have become ever better acquainted with the dangers of excessive dosage and have formulated rules of safety The incautious application of these rays during pregnancy may cause abortion or may injure the fœtus if it survive

Influence of Air Pressure

Many persons are sensitive to changes in the weather Though these changes are associated with rise or fall of the barometer it is not believed that it is the mere oscillations in the air pres ure that are directly responsible for the weather sensitiveness complained of It is apparently only in very rarefied air or very highly compressed air that the changes in pressure cause functional disturbances

When the body is exposed to very high pressures disturbing symptoms aside from those referable to the ears and paranasal sinuses rarely occur unless there is too sudden diminution of the pressure Bridge builders who work in large water tight and air tight cases caissons in laying foundations in deep water run the risk of developing caisson disease unless great care is taken to return only gradually to normal atmospheric pressures They are prone to suffer from pains in the abdomen and in the joints of the extremities the bends from pruritus epistaxis and vomiting In some instances severer syndromes spastic paraplegia a Meniere syndrome make their appearance occasionally especially if circulatory or pulmonary disease have pre-existed fatalities occur

The phenomena are explained through the fact that nitrogen is absorbed by the fluids and tissues of the body when the worker is exposed to high pressure and when these are reduced too rapidly nitrogen gas bubbles develop in the tissue spaces and in the blood and injure tissue elements by the pressure they

exert, or cause gas embolism of smaller vessels with resulting local ischamias That is why laws have been passed requiring slow decompression and by successive stages, of the workers

The danger to deep water divers, who encased in water tight and air tight diving suits have to stay at times under pressures from five to seven times the normal atmospheric pressure, is still greater because of the difficulty or impossibility of providing for slow decompression Prophylaxis here consists in shortening the period of exposure to high pressure in order that the body tissues and fluids do not absorb so much nitrogen

When the body is exposed to very low pressures, the diminished partial pressure of oxygen makes itself felt, dyspnœa and cyanosis develop especially in those not trained, acclimatized to life at low pressures Thus arise mountain sickness among climbers, balloon sickness and aviators sickness at high altitudes, some of the latter provide themselves with oxygen masks for prophylactic purposes

The influences of weather and of climate in general depend largely upon physical components of environment Thus, studies of the relationships of tuberculosis to the environment have indicated that hot climates low altitudes and moist atmospheres are, in general, more unfavorable than their opposites

Influence of Propagated Motion (Kinetic Influences)

Sudden acceleration of motion in any direction by irritation of the vestibular apparatus can cause dizziness and nausea to which rapidly changing optical impressions may also contribute Personal disposition plays a great role some people being very sensitive others very resistant to the influences of changes of propagated motion Sea sickness is the best example of a 'kinetosis", 'car sickness' and 'elevator sickness' are minor forms In the production of sea sickness except in the cases due to auto-suggestion the pitch of a boat is more effective than the roll though worst of all is the combined pitch and roll spoken of as cork screw like motion Susceptibility to sea sickness is said to be absent in children under two years of age and only slight up to the sixth or eighth year of life A few adults, perhaps 3 per cent appear to be almost wholly immune to sea sickness but many who have thought themselves immune have found in extraordinary circumstances that they were really not so Visceroptosis seems to be a predisposing factor Many do not become ill if they stay on deck in the open air whereas in badly ventilated rooms they quickly succumb Mild sedatives like phenobarbital or sodium bromide by lessening the sensitivity of the nerve centres are used by some as preventatives

It is interesting that Bohec has reported that sailors with inborn or acquired immunity to sea sickness sometimes develop land sickness or 'channel

sickness" when at or near the end of a voyage! Though they do not have vertigo they may complain of headache feelings of anxiety anorexia nausea and insomnia to be followed later by great drowsiness

Chemical Components of Environment

Man lives in a chemical as well as a physical environment Thus in the open air he is constantly inhaling oxygen nitrogen and other gases and particles dusts of various sorts and in houses and in industrial establishments the air may be contaminated by many different gaseous substances some of which may be toxic to the respiratory passages occasionally to the skin and often after absorption to the organism as a whole by way of the blood

Again in food and drink a vast number of chemical substances are ingested most of them beneficial some of them harmful when ingested in excessive quantities or when food stuffs have been improperly preserved or prepared

In addition human beings may in certain environmental circumstances be exposed to the action of chemical substances that through their chemical effects may provoke injury or disease or even cause death Such poisons may do harm by the local effects they produce upon the skin or mucous membranes by virtue of their concentration and their physico chemical properties or through their general effects upon the bodily organs after absorption into the blood

The amounts of chemical substances that act upon the body are very important from the standpoint of toxic injury Thus very minute amounts of certain substances (like alkaloids arsenic or potassium cyanide) may be very harmful or fatal doses of from 5 to 50 g of potassium chlorate or potassium nitrate may kill even ordinary foodstuffs may be toxic in large doses for we read in the literature even of water intoxication and a favorite method of committing suicide among the Chinese has been to swallow large quantities of common salt (300 to 500 g) It should be borne in mind too that certain persons may show outspoken symptoms after ingestion of much smaller amounts of certain chemical substances than those that are innocuous to the majority of people owing to excessive sensitivity or so-called idiosyncracy in this connexion we have in recent years become familiar with a whole series of allergic reactions (see chapters on hay fever asthma and serum disease)

Toxic amounts of chemical substances may reach human beings either through ignorance mistake or intention Thus industrial workers may be subject to chronic poisoning inadvertently neither they nor their employers being aware that dangers exist Many persons become gradually addicted to the excessive use of alcohol tobacco coffee or tea or to the morphine cocaine barbital or sodium amytal habit scarcely realizing what they are drifting into Physicians

pharmacists and nurses or their aids occasionally administer poisonous substances entirely by mistake Criminals use poisons with murderous aims Suicides are often due to either impulsive or deliberate self poisoning

Some poisons in small doses produce no evident immediate effects, but long continued exposure to them may result in slow changes in the body and give rise later on to symptoms or increase susceptibility to disease Thus, persons exposed to benzol fumes may after weeks or months give rise to a progressive anæmia and to a hemorrhagic tendency In factories for the manufacture of artificial silk and among certain varnish workers poisonings by organic chlorine preparations may lead to atrophy of the liver and to disturbances of the liver functions The prophylaxis of acute and chronic intoxications has become in recent years one of the most important tasks of preventive medicine In other parts of this treatise the toxicology of the many inorganic poisons and of the organic poisons of industrial, plant and animal origin is discussed

Biological Components of Environment

Human beings are surrounded not only by other persons but also by a host of other living organisms many of them most helpful, others often highly detrimental To these biological components of man's environment ever increasing attention is being paid Among the harmful members are certain of the bacteria the ultra filtrable viruses and the animal parasites

Bacteria often cause intoxications through baneful alterations of food stuffs meat poisonings botulism poisoning through fish molluscs and crustacea and intoxications from milk, cheese eggs, potatoes and preserved foods of various sorts are notable examples

The members of the great group of acute and chronic infectious diseases are, in large part caused by bacterial and protozoan invaders of man from his surroundings some are due definitely to ultra filtrable viruses some, again, are of unknown etiology but presumably are due to as yet undiscovered living infectious agents of some sort

The proof that diphtheria tetanus epidemic cerebrospinal meningitis, cholera, bacillary dysentery, typhoid fever, typhus fever, erysipelas, the septic diseases, tuberculosis, leprosy, plague, undulant fever, tularæmia, gonorrhœa and syphilis are due to cocci bacilli or spirochætes is one of the great triumph of modern medicine Malaria has been shown to be due to a protozoan parasite introduced by the bite of a special mosquito, and yellow fever is due to a living virus introduced by another type of mosquito Acute anterior poliomyelitis and epidemic encephalitis have been proven to be due to invasions by neurotropic ultra filtrable viruses The etiological agents of many infectious diseases among them the acute exanthemata, remain still to be discovered

Psychological Social Economic and Political Components of Environment

The influence of psychological components of environments has received an increasing amount of attention during the past few decades It has become ever more clear that the tendency of the layman to attribute mental disturbances to psychic traumata of various sorts is due in large part to a confusion of cause and effect In the so-called reactive melancholia especially the inherited tendency to depression is often of greater importance than the psychic influence from without to which it may be attributed In Freud's theory of the origin of the psychoneuroses and some psychoses the suppressed complexes may have played a part in altering constitutional make up so that in later life there is an abnormal readiness to react to psychic influences in a pathological way Thus hysterical manifestations are believed by many to be of psychogenic origin in that certain persons expect to be ill in a certain way or desire to appear to have a certain form of ailment in conflicts or in certain situations they tend to react in a characteristic way But recently psychiatrists seem inclined to accept the view that the abnormal mental pictures they see in the neuroses and psychoses that develop after strong psychic influences in the environment such as in earthquakes war social upheavals etc depend more upon the personality make up of the individuals concerned than upon the particular form of the external irritation

Medical literature is full of reports of cases in which the psychic influences attendant upon earthquakes shipwrecks strikes panics explosions fires railway and motor accidents economic crises political upheavals and great religious movements have been regarded as precipitating causes of emotional upsets and of the insanities of various sorts The psychic effects of homesickness of estrangements of isolation of imprisonment of legal entanglements of conflicts in familial and social life of spiritualistic seances and other special situations have been much commented upon But writers have had great difficulty in determining in how far in any given case the psychic influences were responsible and in how far the *anlage* has been responsible Experiences in the Great War especially proved how dangerous it is to speak of pure psychic causal stimuli To the surprise of everybody it was found that the frightful conditions experienced the horrible spectacles witnessed and the fears of injury or death that could not help but exist gave rise to far less psychopathic reaction than many had anticipated indeed not a few persons who before the war had manifested hypochondriacal and psychasthenic symptoms got rid of them instead of finding them increased! And since the war some doubt has become prevalent regarding the etiological influence of fear in the production of the so-called fright psychoses An analysis of many of them has made it clear that pre

pharmacists and nurses or their aids occasionally administer poisonous substances entirely by mistake. Criminals use poisons with murderous aims. Suicides are often due to either impulsive or deliberate self poisoning.

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CHAPTER XIX A

WORK AND FATIGUE

By DONALD A. LAIRD

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Fatigue is not synonymous with work only a portion of the complaints of fatigue can be soundly attributed to work There is in fact a growing body of opinion and experience which indicates that fatigue as ordinarily conceived can be separated from work without productivity suffering This Utopian condition depends upon the cooperation of physicians psychologists and industrialists and is already being approximated in some industrial establishments

FEELINGS OF FATIGUE

To the *patient fatigue* means lassitude weariness muscular tiredness and a disinclination or inability to engage in activity Such a clinical picture obviously may be but a part of the symptom complex of organic involvements and an individual s complaints of fatigue always should be studied first from this point of view

It is now recognized widely that these feelings of fatigue rest more uniformly on a psychoneurotic than on any other foundation[1] Immediately organic causes of fatigue are eliminated attention should be given to psychic factors at work in the individual in fact it is advantageous to make some use of psychotherapy from the first contact with a patient complaining primarily of fatigue Suggestive psychotherapy of the old school is adapted for the early contacts but when the case is found to be clearly psychoneurotic a rational technique of psychoanalysis combined with massage recreation and diet is indicated Psychoneurotic fatigue should be treated seriously with an understanding both that such patients are easy prey for charlatans and that the complaint may be a prodromal symptom of a developing severe psychotic condition

existent states of somatic weakness on the one hand or pre existent desires of hysterical persons on the other, or mixtures of the two were largely responsible for the development of the profound feeling of physical and psychical impotence of those who manifested acute mental disturbances after emotional shocks in the war Many of those who were affected were of hyperthyroid tendency or had exhibited vasomotor instability earlier

Much has been written also about the exhaustion syndromes or fatigue syndromes of the war, occurring after prolonged physical, intellectual or emotional strains Even persons previously healthy might after such excessive fatigue enter a state of extreme lassitude accompanied by feelings of complete indifference apathy or morose depression During such fatigue states illusions and hallucinations were sometimes observed The mechanical excitability of the muscles was increased, the pulse rate became accelerated the blood pressure sometimes rose and there was a tendency to sweating and to paræsthesias These otherwise healthy persons usually recovered completely, if they were able to secure a long period of sleep A most striking thing during the war was the extraordinary capacity of the healthy brain to resist the deleterious influences of severe exhaustion combined with strong excitation of the emotions often too with severe bodily injuries In less healthy brains exhaustion psychoses often appeared Moreover, under the influence of great fatigue epilepsies sometimes developed and latent neurosyphilis or latent dementia paralytica tended to become manifest

Recently, there has been ample opportunity to observe the mode of reaction of people both in Europe and in America to a most severe economic crisis More astonishing perhaps than the suicides and the depressions reported has been the calmness and the brave willingness to adjust to the difficulties of the time it has become in many circles bad form" to complain

In Russia during the past decade, the influence of rapidly changing forms of social and political organization could be witnessed in Italy the influence of fascism and in Germany and Austria the influence of the change from a monarchical government to a republican form has been in evidence In time doubtless we shall have reports of systematic studies of the effects of such influences

Since the opening of the new century, the mental hygiene movement has developed rapidly and the public has been ever better educated in the mental hygiene of childhood of school life and of adulthood It is hoped that through these mental influences and especially through the early conditioning of reflexes and the establishment of desirable behaviour patterns much may be accomplished for general welfare

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accordingly should be versed in the art of dealing with psychoneurotic fatigue as well as in the science of the objective sources of fatigue

Internal Causes of Diminished Capacity for Work

The underlying physiological cause of most objective fatigue which is caused by work is found in the accumulation of lactic acid The use of muscles whether in repeated active contraction as in hammering or in maintaining a particular tonus as in soldiers at attention depend upon the utilization of glycogen Sodium lactates are the principal by products of this utilization which is not an oxidation A large percentage of the lactates are oxidized back into glycogen for further utilization but under the most favorable conditions only approximately 80 per cent of the lactates are oxidized into sugar

The lactic acid accumulates under conditions of heavy work more rapidly than it is oxidized and this is a basic cause of diminished capacity for work With only one member of the body contracting repeatedly to cause an excess of lactates they spread to other portions of the body where they may actually fatigue a relatively unused muscle specialized work thus may cause generalized fatigue[5]

A second factor is found in the accumulation of lactates causing an oxygen debt so that the oxygen taken from inspired air is abnormally high for relatively long periods following the cessation of actual work Some of the individual differences in the susceptibility to fatigue are attributed to variations in the oxygen-carrying power of the blood it has been found that athletic training increases this power appreciably

A third internal factor is that with heavy muscular work a sugar debt may be caused Only a portion of the lactates are oxidized back into glycogen for use as muscle fuel and a marked sugar depletion has been demonstrated following a boat race with university crews at the oars

A fourth internal factor is the loss of body salts through perspiration

The practical management of these internal causes is simple and usually effective The loss of body salts is compensated in many industrial operations by the addition of common table salt to the drinking water this is done especially in the case of miners but merits a more general adoption The sugar debt is taken care of in other establishments by canteens from which the workers may secure carbohydrate rich foods especially candies and sugar wafers during working hours or at a specified time during each work spell

The accumulation of lactic acid and the oxygen debt are to be attacked principally by the provision of rest periods Industry gradually is adopting rest periods on its own initiative since it is demonstrated that their use increases output The ratio of work time to rest time should be determined by

In the more mild instances psychically-caused feelings of fatigue may be due to monotonous work, a desire to be engaged in other work, dislike of foremen or supervisors, worry about economic security, concern over home conditions and kindred situations and emotions[3]

Diminished Capacity for Work

Industrial fatigue, in the strict sense, is the diminished capacity for work that is caused by the work As output per unit of time begins to decline, fatigue has set in according to this strict conception, although the rise and fall of output bears little direct relation to the subjective feelings of fatigue[4] Considering the output of work as an objective criterion of fatigue, the work curve becomes also the fatigue curve Although this approach neglects largely the individual s feelings of fatigue and although the work or fatigue curve of an actual industrial occupation may be falsified by either 'soldiering (or "hanging it out) or by an inadequate flow of work materials to the worker, this approach nevertheless is the more scientific and objective and has yielded more extensive and practical results than the subjective study of the feelings of fatigue It is accepted generally that the work curve gives a close approximation to the actual physical fatigue of the worker with little complication by psychoneurotic symptoms which often are confused with physical fatigue

The general course of the work or fatigue curve during the ordinary work day is a rise early in the work spell and a decline the last hour or two of the work spell The initial rise is a warming up phenomenon and is found both in mental and physical work In some tasks and under favorable working conditions there is a persistent increase from hour to hour in output during the first or the forenoon work spell Conditions are to be considered fatiguing when they make the warming up time longer than usual, or when they make the decline late in the work period either more marked or earlier in onset than usual

Total production per work spell is a less sensitive indicator, which is sometimes used to discover fatiguing conditions or methods of work More recently instrumental measurements of the human being at work have been used to assist in the discovery of factors deleterious to fatigueless work The metabolic increment above resting occasioned by work, body sway in the Romberg position and some psychological tests involving the use of apparatus have been used to approach the problem of work and fatigue from this angle

All of these methods have supplanted largely the use of the individual s personal feelings of fatigue as a method of discovering the real sources of fatigue from work The physician however, has to deal with feelings of fatigue perhaps more frequently than with *fatigue that has an objective cause* and

effects are present when the noise is more than the loudness of ordinary conversation or about 40 decibels intensity The third factor has been demonstrated for a loudness of 60 decibel or more which is approximately the amount heard by the passenger on a trolley car A transfer to a quieter work place will help in many cases of fatigue The work place itself can be quieted to a remarkable degree by acoustical experts using sound absorbing material[7]

Vibration — Vibration usually is linked closely with noise as a cause of fatigue but the former appears to operate by making work more difficult through the repeated mechanical displacement of hands from the work as well as through the too long continued general massage

Lighting — Inadequate lighting causes diminished capacity for work largely through the secondary effects of eye strain The light should be of a uniform distribution relatively shadowless and bright sources of light should not appear in the field of vision The optimum illumination for various types of work is given by Luckiesh[8] Uncorrected eye defects also are a common cause of generalized fatigue

Ventilation — As the cooling power of the air becomes too marked or too diminished an added and a fatiguing burden is thrown on the heat regulating mechanisms of the body Temperature of the air humidity and the motion of the air are the chief elements determining its cooling power A room temperature of 68 F is the optimum for least fatigue among sedentary workers all other things being equal Active manual workers may have their optimum as much as 10° F lower than this As the temperature rises above this optimum its cooling power may be increased by the use of fans or agitators or by altering the moisture content Fatigue from an increased carbon dioxide content of the air is not found even in deep mines Empirically determined tables for determining the cooling power of various air conditions have been prepared by the United States Bureau of Mines laboratory at Pittsburgh[9]

Methods of Work — Possibly the principal external source of fatigue among the industrial population is improper methods of working management as well as labor is responsible for this condition In recent years however some of the outstanding business organizations have installed special planning and training departments for discovering the least fatiguing methods of work and for training new employees in these methods The Society of Industrial Engineers has a special International Fatigue Committee organized for promulgating such work Professor George Shepard of Purdue University is chairman of this committee The National Institute of Industrial Psychology London England has had a more varied and more successful experience in developing less fatiguing methods of work than any other organization[10]

Day and Night Work — Data show that night work is more fatiguing than day work Generally this is attributed partly to poorer illumination during the

experiment, if the work time is too short, the benefits of warming up are missed and if the rest time is too short, insufficient progress is made in oxidizing or eliminating lactates In light dextrous work such as folding handkerchiefs a ratio of five minutes work to one minute rest has been found most effective In the case of mental work the work period ordinarily should be of at least an hour before a rest pause is taken Reports of industrial experiments with various ratios of work and rest can be obtained from the Industrial Health Research Board, London

Large amounts of phosphates have been used to counteract the fatigue of soldiers caused by forced marches These have yielded favorable results The theory upon which phosphates were used was that they would provide the nervous system with fresh materials for its phospholipins, control experiments however, have indicated that the beneficial results were due rather to the laxative effect

Although our knowledge on the point is not clear, it is doubtful if work impairs nervous tissues in the ordinary course of events, but the accumulation of lactates may impair the functioning of the end plates

The use of adrenalin in counteracting fatigue should be very cautious Primary attention should be given to the four internal factors mentioned as well as to the general health of the individual Endocrine imbalance may be a factor in some cases

The female periodical functions bear a closer relation to feelings of fatigue than they do to actually diminished capacity for work Except in instances of disordered menses periodical functions may be disregarded largely in their relationship to work and fatigue

EXTERNAL CAUSES OF DIMINISHED CAPACITY FOR WORK

Posture —Poor posture, often forced by the arrangement of working materials and tools, is a common cause of unnecessary fatigue Stooping continued standing and bending are included under this heading All cause needless muscular tension and hamper the circulation to some extent as well as lessening the volume of air taken into the lungs under some circumstances Benches and machines should be arranged so that the worker can either sit or stand as his sensations of fatigue prompt him Stooping stretching and bending also should be avoided by the proper arrangement of tools and materials[6]

Noise —Noise causes fatigue by (*a*) requiring more effort to talk loud enough to be heard above the noise (*b*) requiring a closer amount of attention and consequent muscular tension to listen above the din and (*c*) by causing a physiological fear reaction with resulting increase in blood pressure, striped muscular tonus and a lessening of the peristaltic contractions The first two

CHAPTER XX

MEDICAL-SOCIAL SERVICE AS A FACTOR IN THE DIAGNOSIS AND TREATMENT OF DISEASE

BY RICHARD C CABOT

I

BOTH in the causation and the relief of disease bacteria and their products together with certain physical and chemical agents play the chief parts But they are not the whole Psychological industrial and educational factors for instance are also of some importance Medical social service a branch of social work in general deals with these factors and is therefore a useful tool in the medical kit

In war medicine these factors are at their minimum and medical social service is relatively unimportant there On the other hand in the hospitals of great cities especially in Out Patient work the social economic racial domestic and other influences dealt with by medical social workers are at their maximum Hence good medical practice is there impossible or at least improbable without the social worker s aid

In private practice and especially in the general practice of country districts and small towns the successful doctor usually does the social work himself He deals as best he can with the mental emotional and industrial life of his patients in its bearings on their diseases He is his own social worker as he is his own surgeon laboratory man and radiologist This is possible because he knows each patient (and often his family) individually He can see how each sufferer s maladies are the joint product of physical chemical and bacterial agencies *and* of the worries deprivations work conditions and home conditions under which he lives

But in the organized medical work of a great hospital or a metro politan public school it is impossible for the physician to know all the important facts about his patient unless those facts lie on the surface The cut finger the diphtheritic membrane the gonorrheal discharge he can see but the root causes of the stomach troubles backaches debilitated states which bring nearly half the patients to the hospital he cannot see at once and has neither the time nor the means to investigate thor

night periods, but principally to the inability to secure restful sleep in the day time the light noise and other activities of the daytime appear to conspire to make sleep less restful As a rule it is not desirable for a worker to continue on night work for a long period, both from the point of view of general health as well as fatigue

Sleep and Work — A reduced sleep schedule has been found to increase fatigue resulting from routine work The patient s sleep always should be surveyed both for length and for quality of sleep As a rule it is preferable to attempt to improve the general sleeping conditions rather than to use sedatives[11,12,13]

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clinic and in the child s home can see what is going on and can get things done—or at least ascertain that they are not done and that no good results can therefore be looked for

In the neurological clinic the hemiplegics arteriosclerotics paretics and epileptics must be gotten into institutions or their home companions must be shown the little that can be done to ease and cheer their lives By teaching and occupation the social worker can save them much suffering though medicine and surgery are practically helpless

The functional cases the tics stammerers psychoneurotics need re education of a type which no clinic physician has time and few have ability to give A properly trained social worker by intensive effort can do wonders for a few pa ients and accomplish substantial good for many more

Still more important is the social worker as a magnet or focal point to which are drawn the functional neuroses usually hidden in the gynecological or general medical clinics where they are maltreated under diagnoses like gastritis constipation ptosis (gastric intestinal or uterine) endometritis anemia and debility In the orthopedic in the general medical clinic and in the departments of dermatology syphilis and tuberculosis social service work is important but somewhat less essential than in pediatrics and neurology

In the surgical and throat departments there is still less need of anything beyond what doctors and nurses can give

III

What the social worker does for disease can be grouped under four headings (*a*) Discovery (*b*) prevention (*c*) education (*d*) disposition

The discovery of concealed nests foci or cases of disease through visits to the patient s home workshop or school can be carried out by health officers or public health nurses as well as by social workers especially when the data sought for are obvious Thus hidden nests of malaria uncinariasis pellagra lead poisoning and tuberculosis are now and then brought to light by public officials

Put in hospital work where the single case of phthisis rickets syphilis or occupational disease is the natural starting point and spur to the search for nests of cases like it we need someone who can act as the doctor s and the hospital s agent following a clue held there. Because the social worker is not a public official and comes from an institution which tries to assist rather than to discipline or check people

oughly Yet without finding root causes his treatment is bound to be a failure and his daily work a waste of time

Whenever a person s sickness *arises out of the way he lives* (rather than out of some acute catastrophe like an explosion or a railway accident) the doctor must know how he lives But in hospitals or public schools the doctor has no chance to grasp these essential factors Hence the need of such help as a good social worker can give

A child is pale thin listless in school work Physical examination may show no clues for diagnosis Questioning seldom helps But a series of home visits by a woman who has the faculty of getting along pleasantly with school children and their families who can investigate the details of diet sleeping rooms and sleeping habits the opportunities for contagion the possible bearings of family income, family discord or paternal alcoholism on the children's health —this I say may bring to light the facts on which rational diagnosis and treatment can be based

So far I have written of social work chiefly in diagnosis and in etiology as a part of diagnosis But social work bears also on prognosis and on treatment If malnutrition, dyspepsia headaches gonorrheal vulvovaginitis scabies or rheumatism are based on home conditions which we are practically powerless to change, then the prognosis is a blind alley no thoroughfare and we can turn our energies elsewhere.

If, on the other hand the causative conditions can be changed by social service work then that is the treatment indicated Sometimes really brilliant therapeutics can be thus achieved

II

I have already tried to show as under a low power of the micro scope the field of medical social work and the tools likely to be useful there Seen in more detail its place and methods are as follows

In the neurological and psychiatric clinics of a hospital Out Patient Department and in the pediatric clinic almost every case needs study and treatment by a social worker acting under direction of the Clinic Chief To feed babies to get older children properly nourished and fit to resist the common infections with success is a matter of multi tudinous detail An exact knowledge of how the child lives eats sleeps works and plays is essential The doctor cannot get this knowl edge satisfactorily by questioning the child or its mother Still less can he be sure that his directions and prescriptions are carried out exactly and persistently He is at arm's length from his case He cannot handle it The social worker acting as his agent both in the

stands him and feels a genuine interest in him can accomplish more therapeutic education than anyone else now in sight

By the disposition of patients I mean here the process of getting them into institutions of getting financial or other aid for them through cooperation with other charitable agencies or with private individuals all of these which are available in her district the social worker first lists and sizes up then learns to use

Hospitals special and general sanitoria convalescent homes homes for the aged special funds for vacations for recreation for pure milk for trade training (as in the case of mutilated persons) exemplify the tools which the social worker learns to use more or less effectively for hospital patients

IV

The social service department of a hospital should function as the X ray department does—not as an independent agent but as part of a team under the direction of one guiding mind The facts elicited by the social worker s studies talks and visits should (like X ray data) be pooled with the data of physical examinations the laboratory findings etc Then they are appreciated and of value not otherwise

So with her educational therapy It will often go wide of the mark unless it is supervised (like X ray treatment or massage) by the doctor in charge of the case

To turn a patient over to the social service department once for all is a common but wholly mistaken practice

Why has the work described here arisen only since 1905?

Because of the development of big Out Patient Clinics where team work of many takes the place of one s doctor s attempt to do everything himself The development of diagnostic and therapeutic teams and with this the stratification of medical jobs so that untrained people can do much of the job leaving the doctor for his expert work has helped to show us how many sided is the task of helping a sick person towards recovery

In the division of labor thus developed place is found for one who deals in details who knows the patient in his home his worl and his school and who gradually becomes competent to trace out and record the mental elements present in all organic disease as well as in functional or neurotic maladies

This is the most important point in the whole matter Mental elements in the causation in the symptomatology in the prognosis and treatment of disease are recognized today more fully than ever before

We know today more than we ever did before what worry fear

she * is in a good position psychologically to get the facts she is after She is welcome People are not afraid of her and are less likely to lie to her than to a public health official

Besides the discovery of *new* cases of disease the social worker by her greater intimacy with the patient's family and by her chance to talk with him uninterrupted in his home and for a good while, may find *new features* in the cases already known and treated Omissions in the history new light on its interpretation further links in the chain of causation may be brought out thus Why cannot the doctor do this better? First, because under present conditions of hospital organization he has not the time for home visits i e he is more useful to more people by spending his time on such diagnoses and treatments as he can offer in conjunction with the other elements of the hospital team consultants assistants machines and laboratories This ties him down

Moreover, he is not usually an expert in the give and take of intimate personal intercourse with people of the type who consult him at a free hospital He cannot get at them as well, understand them as quickly or as far as a well trained and sympathetic woman can

Prevention through social worker's efforts springs from the discovery of incipient cases on home visits and through the detailed hygienic explanations and therapeutic teaching presently to be referred to She may thus prevent the relapses of mental disease of peptic ulcer of flat foot of industrial dermatitis and to this extent prevent the existence of new cases of disease of "old" patients

Education in the details of diet sleeping arrangements, exercise recreation and the other departments of hygiene must be fitted to the individual like a suit of clothes if it is to be of use to him General rules are of little value especially if presented in printed circulars and in a hasty offhand way The rules must be applied reshaped and modified to suit the individual's needs after these needs have been studied with care Moreover since these hygienic rules often call for the reform of tough old habit one must use every effort to get a *dynamic* sufficient to make the patient put himself to so much trouble The fear of disease and the doctor's authority can accomplish something towards making a man change his habits of diet, of work or of thought But usually we need also the persuasive force of someone who cares for the individual sufferer and is believed by him to understand his circumstances his difficulties and his point of view The medical social worker acting for the doctor and transmitting his authority and his directions to a patient who believes that she under

* Why a woman is preferable I will try to show later

CHAPTER XX A

PSYCHOSOMATIC MEDICINE

By EDWARD WEISS

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Introduction

Psychosomatic is a new term but it describes an approach to medicine as old as the art of healing itself. It is not a speciality but rather a point of view which

grief and other emotional strains can do in modifying and augmenting and prolonging disease We also know something of what peace of mind habits of concentration, recreative enjoyment satisfaction in work, friendship or religion can do to banish or to alleviate disease

No medical social worker is an expert fit to succeed often in under standing or manipulating all these delicate and pervasive forces But when she is born for her job and then trained on it, she can contribute perhaps as much to the hospital team work as any single person in it

It is in organized medicine then as we have it in the best modern hospitals sanitoria schools and factories that medical social service has its chief function Whenever medical organization takes a step forward whenever group medicine in any form progresses, the sort of aid and technique here described will I believe find a part

much concerned with such patients It is estimated reliably that about a third of the patients who consult a physician fall into this group These are the so-called purely functional problems of medical practice

(2) Another large group of patients who consult a physician have symptoms that are in part dependent upon emotional factors even though organic changes of non psychogenic origin are present This second group is even more important than the first from the standpoint of diagnosis and treatment These psychosomatic problems often are very complicated and because serious organic disease may be present the psychic factor is capable of doing more damage than in the first group This phase of the subject is especially well illustrated by many instances of organic heart disease For while a neurotic with a normal heart may suffer a great deal subjectively and may even have a disturbance of cardiac function marked by various forms of arrhythmia the heart certainly in the majority of such patients remains structurally healthy But the neurotic patient who has organic heart disease may add a real burden to the work of his heart either through constant tension of psychic origin or more especially by means of acute episodes of emotional origin This may hasten a cardiac breakdown which might be postponed indefinitely if there were no psychic stress Thus the psychic factors may be even more important than the physical in producing incapacity

(3) Psychosomatic medicine is much interested in disorders generally considered wholly within the realm of physical disease which have to do with the vegetative nervous system such as migraine asthma peptic ulcer and essential hypertension It is believed that psychic factors may be of great importance in their etiology and even more importantly in their management

(4) Here we touch upon a fourth problem related to 2 and 3 in which studies are just beginning to be made that is the possible relationship of psychological disturbances to structural alteration The viewpoint of disease bequeathed to us from the nineteenth century could be indicated in the following formula

Cellular disease → Structural alteration → Physiological (or functional) disturbance

In the twentieth century this formula underwent alteration in some situations For example in essential hypertension and vascular disease the formula was altered to read

Functional disturbance → Cellular disease → Structural alteration

We are still in the dark as to what may precede the functional disturbance as in the example just cited of essential hypertension and the resulting vascular disease It seems possible that future investigations will permit us to say that it is possible for a psychological disturbance to antedate the functional alteration Then the formula would read

applies to all aspects of medicine and surgery It does not mean to study the soma less, it only means to study the psyche more Its subject matter is founded on the important advances in physical medicine as well as on the biologically oriented psychology of Freud without whose epochal discoveries no work on psychosomatic medicine could be attempted Following these discoveries Felix Deutsch then of Vienna and Jelliffe in America applied this new psychopathology to general medical problems Later Alexander and his associates at the Chicago Institute of Psychoanalysis Karl and William Menninger of Topeka, Halliday of Scotland and Dunbar and her associates at the Presbyterian Hospital in New York by their important researches added materially to our knowledge of this subject In 1935 Dunbar in addition to her valuable studies performed the great service of collecting the widely scattered literature in this field under the title Emotions and Bodily Changes[9] The epochal discoveries of Freud the researches mentioned and the compilation of literature by Dunbar as well as the contributions of many others are all used freely in the following discussion

Physicians have always known that the emotional life had something to do with illness but *the structural concepts introduced by Virchow* led to the separation of illness from the psyche of man and to a consideration of disease as only a disorder of organs and cells With this separation of diseases into many different ailments came the development of specialists to attend to all of these distinct diseases With the specialists came the introduction of instruments of precision and the mechanization of medicine began Medicine now contented itself with *the study of the organism as a physiological mechanism* impressed by blood chemistry, electrocardiography and other methods of physical investigation but unimpressed by and indeed often holding in contempt the psychological background of the patient which was considered not so scientific as the results of laboratory studies This period may in truth be referred to as the 'machine age in medicine' It is not to be denied that remarkable developments have *occurred during this period of laboratory ascendancy* but it also must be admitted that the emotional side of illness has been almost entirely neglected

Psychosomatic Problems in the Practice of Medicine

Defined as bodily disorders whose nature can be appreciated only when emotional factors are investigated in addition to physical factors psychosomatic affections can be studied in the following manner

(1) Between the small number of obviously psychotic persons whom a physician sees and the larger number of patients who are sick solely because of physical disease in which emotional factors play no part are a vast number of sick people who are not 'out of their minds' and yet who do not have any definite bodily disease to account for their illness Psychosomatic medicine is

is daily work He must know a little about gross disorders of the mind but only enough to see clearly that these extreme alterations are merely exaggeration of trends and reactions that he may observe in himself in his friends in his patients If a physician is once persuaded to look within himself and to learn to identify unaccountable variations in mood and energy as the analogue of a manic-depressive cycle the habit of ascribing failure and disappointment to ill luck or persecution as the promptings of paranoia day dreams (in which satisfaction is secured for the rubs and indignities of life and retributive disaster showered upon enemies) as the harmless whisperings of schizophrenia certain exaggerated reactions as the masks for defeats and inadequacies various somatic symptoms as excuses for retreat from difficult or unpleasant situations he will forever have an enduring interest in psychiatry

Suspicion of Physical Disease

Sometimes the patient is told that the physician does not think that anything is the matter but suspicion is cast upon some organ or system which needs watching and care For example the patient with symptoms referred to the heart region is told that his heart is all right Nevertheless he is cautioned to rest medicine is given and each time that he visits the physician his heart is examined again or his blood pressure is taken It is impossible to eradicate the suspicion of organic disease under such circumstances This point will be considered later but here it may be emphasized that in dealing with the majority of functional problems we must examine thoroughly satisfy ourselves as to the absence of physical changes and then stop examining with the firm statement You have no evidence of organic disease

Pathological Curiosities

Very frequently following thorough study by means of the usual medical history physical examination and laboratory investigation some pathologic curiosity * is discovered which really has nothing to do with the illness but the patient then is treated from the standpoint of disease and is subjected to unnecessary medical or surgical treatment which in many instances intensifies the neurotic condition For example a common cause of fatigue is not infection but emotional conflict which uses up so much energy that little is left for other purposes A patient with chronic fatigue may be studied from every possible physical standpoint and finally especially in the presence of long continued low fever suspicion rests upon minimal and obsolete tuberculosis of the lungs

* By pathologic curiosity is meant some congenital or acquired lesion that has no significance from the standpoint of the present illness

Psychological disturbances → Functional impairment → Cellular disease → Structural alteration

With the last problem, however, this discussion is not greatly concerned. It is restricted for the most part to known psychosomatic relationships—in other words, a discussion of clinical problems for which there are immediate practical applications.

THE PRESENT MANAGEMENT OF PSYCHOSOMATIC PROBLEMS

The Illness Is "Functional"

How does modern medicine handle these patients? When we review our present management, we find that the patients in group (1) are commonly told that no organic disease is present and that the whole thing is "functional." They are dismissed often without further care, only to land eventually in the hands of some irregular practitioner or quack healer. Certainly in dealing with many of these patients it is necessary to do more than assure the patient of the absence of physical disease. Nor does it do to dismiss a patient with the statement that his illness is "functional." To the physician this term usually means psychogenic, although he does not always admit it, even to himself. All kinds of twists and turns are taken to avoid the use of the hated term psychogenic. Often neurogenic replaces it and thus the physician is permitted to hold on to the notion that somehow there is a physical answer to the problem. This point will be discussed shortly.

Hamman[1] has written with a great deal of understanding on this subject: "When I was a student, the course in psychiatry consisted of lectures upon insanity and the demonstration of patients with gross disorders of thought and conduct. I had no interest in the topics and the patients distressed and disturbed me. I was greatly relieved when the course was over and never dreamed that I should find any occasion upon which to apply what I had heard and seen. I fully determined to have nothing further to do with psychiatry and unfortunately I held very obstinately to this determination. As a matter of fact, I still hold to it as regards what I *then considered to be the* province of psychiatry. I say that this determination was unfortunate because it prevented me from understanding what is the true domain of psychiatry, and so blinded me that it was many years before I could see the fruitful application of psychiatry to the daily problems of practice. In a word, the practicing physician is not at all interested in what he scornfully regards as the medicine of the madhouse and the asylum, but he is vitally interested in what we may call every day psychiatry. At least he becomes interested in it when his interest is properly aroused by the demonstration of the importance and value of the application of psychiatry to

apprehension or by evidences of physical nervousness betray the fact that neurosis is present Their approach to the emotional problem is apt to consist of *the question Are you worried about anything? Unfortunately most neu*rotics do not betray their neurosis in their appearance nor is the approach to their emotional problem so simple that the direct question Are you worried about anything? , will produce material of importance

Diagnostic Problems in Psychosomatic Medicine

More specifically then what are some of the diagnostic and therapeutic problems of psychosomatic medicine and how are they to be approached?

First there is the failure to recognize neurosis and treatment of the patient as organically diseased This happens most frequently as already suggested because modern clinical medicine attempts to establish the diagnosis of functional disease by ruling out organic disease through medical history physical examination and laboratory investigation The point that I particularly wish to make is that the diagnosis of functional illness must be established not simply by exclusion of organic disease but on its own characteristics as well In other words neurosis has its own distinctive features to be discovered by psychosomatic study for only in this way can serious errors in diagnosis and treatment be avoided If the above statements are admitted to be correct it must follow that personality study is just as important in the problems of illness as laboratory investigation

This kind of approach will do a great deal to relieve the fear of the physician that he is missing something organic because it will supply him with additional information to confirm his diagnosis of functional disease It is perfectly true of course that structural alterations can be overlooked and the patient treated only as a functional case which is the reverse of the situation above mentioned Physicians are constantly harassed by this fear of overlooking organic disease They are of the opinion when dealing with this class of patients that the structural disease is hidden and will come to light with the passage of time Again this may be true but in the majority of instances is not

A recent study from the Mayo Clinic is illuminating in this regard Macy and Allen[2] studied the records of 235 patients approximately six years after the diagnosis of chronic nervous exhaustion had been made with the idea that if the clinical picture at the first examination was due to unrecognized organic disease such organic disease should be detected by subsequent examinations over a period of years The accuracy of the diagnosis proved to be 94 per cent which seems to indicate that this kind of functional illness at any rate is not due to organic disease It is interesting to note in passing that 289 separate operations had been performed on 200 patients of the group that they studied

Long periods of rest in bed or sanitarium may follow. The error in the study of such cases is the fixation on physical factors and the absence of attention to emotional factors so that the physician himself becomes a "pathogenic agent" in helping to fix the neurosis.

In other words the attitude of modern medicine is not so very different toward these patients from that described in 1884 by Clifford Allbutt [2] the great English clinician who said in speaking of the visceral neuroses: "A neuralgic woman seems thus to be peculiarly unfortunate. However bitter and repeated may be her visceral neuralgias she is told either that she is hysterical or that it is all uterus. *In the first place she is comparatively fortunate, for she is only slighted; in the* second case she is entangled in the net of the gynecologist, who finds her uterus, like her nose, is a little on one side, or again, like that organ, is running a little, or it is as flabby as her biceps, so that the unhappy viscus is impaled upon a stem or perched upon a prop, or is painted with carbolic acid every week in the year except *during the long vacation when the gynecologist is grouse shooting or* salmon catching, or leading the fashion in the Upper Engadine. Her mind thus fastened to a more or less nasty mystery becomes newly apprehensive and physically introspective and the morbid chains are riveted more strongly than ever. Arraign the uterus, and you fix in the woman the arrow *of hypochondria*; it may be for life."

The Organic Tradition in Medicine

As a consequence of this structural and physiological tradition in medicine a large number of physicians pride themselves upon their unwillingness to concede the absence of physical disease when dealing with an obscure illness. In discussing such a patient they are apt to say "but there must be something the matter," meaning that there must be a physical basis for the illness. And they furthermore believe that future researches along the lines of physical *medicine* will eventually uncover the hidden causes, infectious, allergic, endocrine or metabolic, responsible for such obscure illnesses.

Still another group of physicians are willing to believe that psychic factors have something to do with illness but they have only a vague notion of the part that such factors play. These physicians recognize that there is a "neurogenic factor" or a "large nervous element" present but they look upon this feature as a secondary one and probably a consequence of the physical disorder. While freely acknowledging the relation of psychic causes to such physiological *phenomena as blushing, weeping, gooseflesh, vomiting and diarrhea,* nevertheless they find it difficult to believe that more prolonged, chronic disturbances of a physiological nature possibly can be psychic in origin.

They are the physicians who often remark about a patient, "but he does not look neurotic", perhaps imagining that such a patient should by his general

the same approach Thus in peptic ulcer we must think (1) of the individual what kind of person is he? (predisposition physical and psychological) (2) of the environment what has he met? (tobacco and food social and psychological problems) and (3) of mechanism what happened? (vascular supply hyper acidity hypermotility etc)

Here the psychic element is an integral part of the study one of many and diverse etiological factors emerging at various levels of the personality development

At this point it may not be amiss to quote further from Halliday in regard to that long confused subject functional versus organic disease

Functional and Organic

Another source of obscurity is to confuse the technique of approach with the object of study A common example is the mysterious phrase mind and body This seems to indicate that an individual is composed of two distinct and contrasted entities a mind entity and a body entity If the phrase has any meaning it is this the individual may be studied by a psychological approach and the individual may be studied by a structural or physical approach It is our techniques or methods of investigation which are diverse and multiple not the individual who is a unity

The words functional and organic suggest that illness may be divided into two distinct kinds and much has been written on this faulty premise For example it has been stated that if an unorthodox healer cures a patient the illness must have been functional and presumably not the concern of the scientific medical man who deals only in true or organic illness Again it has been stated that the word functional is applicable to a morbid process which is reversible But what of lobar pneumonia warts and on occasion even lipoma? A little consideration shows that the words organic and functional are merely examples of technical slang which express in convenient form the following In certain illnesses or in certain *stages of these illnesses a structural* technique or approach e g anatomical histological provides a positive finding in slang terms the illness is organic In other illnesses the application of the structural approach provides a negative finding whereas the application of other techniques of approach provides a positive finding in slang terms the illness is functional Many writers failing to appreciate the only meaning which can be given to these terms seem to have imagined that by using them a fundamental etiological basis for the division of illness has been achieved

The following diagrams are used frequently in illustrating this topic Fig 1 illustrates the usual *approach in the study of illness* which presumably will lead to a diagnosis It consists of the bare facts of the medical history the physical

The "Either-Or" Concept

When emotional factors are associated with actual 'organic' changes, too little attention is paid to the emotional factors The feeling exists and the statement is made that "the physical findings are sufficient to account for the illness" In this connection let me again emphasize that just as we cannot limit ourselves simply to the exclusion of organic" disease in dealing with the purely 'functional group, so even more importantly in the second group is there the necessity for not resting content with the finding of an 'organic" lesion The day is near at hand for the final outmoding of the "either or' concept, either functional or organic in diagnosis and to place in its stead the idea of how much of one and how much of the other, that is, how much of the problem is emotional and how much is physical and what is the relationship between them This is truly the psychosomatic concept of medicine

In a well written and remarkably lucid consideration of the "cause of illnes Halliday[4] indicated the approach to this complicated problem with a simple illustration

Let us take says Halliday a fragment of conversation which may be over heard when a toddler begins to howl in the street

> Onlooker to mother Why is he crying?
> Mother Oh he cries at anything he is just a baby
> Small brother 'He saw a cat and it frightened him
> Onlooker 'Well he has got a fine pair of lungs anyway '

"These remarks provide an explanation of the child's mode of behavior in terms of the three fields of etiological discourse In the field of the *individual* the cause is announced to be the characteristic of 'being a baby' in the field of *environment* the encounter with a cat in the field of *mechanism* the lungs in their instrumental perfection It will be noted that if any mode of behavior is to take place cause must operate in all three fields at a particular point in time In the example quoted we may assume that the behaviour called crying would not have appeared in the absence of (a) the characteristic of being a baby or (b) the environment factor of the cat, or (c) the mechanism integrity of the respiratory organs '

Halliday then explains that when the findings as to cause in each of the three fields of 'etiological discourse can be related to one another we may say that the illness is explained Thus in diphtheria 'the cause in the first field is the characteristic summarized by the phrase being Schick positive', cause in the second field is an encounter with the diphtheria bacillus cause in the third field is the toxin produced on the fauces

When we think in terms of the psychosomatic point of view, we must employ

other words besides excluding physical disease in the one case and correctly evaluating the part it plays in another it is of the greatest importance to know the patient's ability to adjust to certain life situations his pattern of reacting to them, the degree of anxiety in his make up and the nature and seriousness of his conflicts Psychosomatic study is necessary if we are to establish a specific relationship of the psychic situation to the personality of the individual Just as the typhoid bacillus specific for typhoid fever depends upon the susceptibility of the individual so does specificity of the psychic event depend upon personality structure of the person To make such studies one must have some training in psychopathology When psychopathology is given an equal place with tissue pathology in our medical curriculum and is as well taught we will finally realize that psychotherapy is an integral part of our medical discipline

Psychopathology

It would seem that we are rapidly approaching such an understanding The great impetus given to this subject by military medicine surely will result in the proper emphasis in medical teaching It can be truly said that World War I established psychiatry on a firm scientific basis and World War II is seeing its final integration into general medicine in other words psychosomatic medicine When this integration has been satisfactorily accomplished there will no longer be need for the term psychosomatic both parts of the term will be implicit in the word medicine

It is impossible in a short discussion to cover the subject of psychopathology Only a few principles can be mentioned There is no sharp line between normal and neurotic Anyone may break under pressure in other words become neurotic Witness the combat neuroses of World War II robust men with previously healthy personalities succumbed to combat fatigue when enough pressure was put upon them The same thing is true in civil life although not so common Generally speaking persons who develop severe psychosomatic disorders or pronounced neurotic disturbances are people who have been predisposed by psychopathology established early in life In other words an adult neurosis depends to a great extent upon a childhood neurosis

Influence of Childhood Environment — A point of view which I have tried to stress is that for the most part psychotherapy is necessary because our educational processes are confined to the intellect In other words our children receive scientific management from an intellectual standpoint but for a variety of reasons mainly constitutional and family influences the emotional growth is stunted It is the retarded emotional development which is fundamentally responsible for psychosomatic illness In other words if the intellectual age and the emotional age differ sharply the background for illness of psychological origin

examination and the various laboratory investigations It is diagnosis by exclusion and fails in so many instances simply because the life situation of the patient, in other words, a study of the emotional life which may provide the key to the solution of the problem, is neglected completely or at most investigated inadequately The proper psychosomatic approach is shown in Fig 2 where the personality study occurs at the same time as the physical and laboratory study

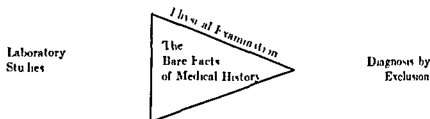


Fig 1*

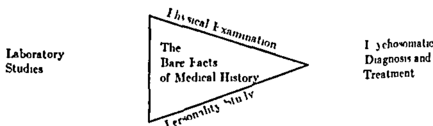


Fig 2

The Nature of Emotional Problems

We know that these patients have been badly handled Can we do any better? What is the matter with them and how should they be treated? First of all let us say that these patients are suffering from disturbances in their emotional lives that is the illness is wholly or in part of psychological origin and can be studied satisfactorily and treated only if this factor is dealt with adequately The ill health arises in a predisposed individual usually from long standing dissatisfactions in the business social or home life, and this failure of adjustment to environment is manifested by a disturbance in some part of the personality either as bodily symptoms of various kinds capable of mimicking almost any disease or as affections of the spirit resulting in attacks of anxiety, obsessions phobias depression and other disturbances of mood What is not so generally realized is that the mere discovery of the so-called dissatisfactions or unpleasant occurrences in the life situation of the individual is not a sufficient explanation nor even an adequate indication of the psychic background of the illness In

* From Weiss E and English O S Psychosomatic Medicine p 7[10]

as the growth processes advance During the first months of life the body needs food and warmth not only because of their importance for physical growth but also for emotional satisfaction The world of the infant is small and what would seem to be of little consequence in the life of the adult may be of primary importance in his life

The Feeding Process — The sensual pleasure derived from the feeding process is an example The total nutritional process will leave a pleasant memory impression upon the mind if the good will and esteem of those who take care of the child are added to the feeding process A sufficiency of food of the right kind given at regular intervals and administered by one who loves the child does much to lay the groundwork for a relaxed personality which feels the world to be a friendly place Thus the nutritional process a feeling of security and the capacity to love are blended harmoniously

If on the other hand there is insufficient food or a sudden change in the type of food or method of feeding or if there is impatience or hostility on the part of the one who feeds the child then the distress of hunger or of cold or the lack of emotional warmth produce anxiety There seems to be a blind sense which we may be permitted to call instinct that if such conditions continue long enough death will ensue In the beginning this apprehension that something threatens the integrity of the self is a reflex pattern and as a matter of fact much of it remains reflex throughout life An important part of the therapeutic educational process is the effort to help the individual to understand the source of his anxiety and to teach him what he must do to relieve it It is fundamental to our understanding of personality development to realize how much basic insecurity and resulting anxiety may occur through deprivation of food warmth or love or through misunderstanding of the physiological rhythms during the early weeks and months of life and that such difficult situations in the life of a child will produce anxiety through a definite physiological mechanism

The Components of Anxiety — Anxiety has two elements a psychic and a somatic or physiological component The psychic component of anxiety is the sensory cortical registration of displeasure and apprehension the instinctual awareness that something is wrong and the somatic component is the motor response of rapid heart action rapid or embarrassed respiration flushing perspiration and even a disturbance in the function of the gastrointestinal tract Anxiety can make its effects felt in every tissue of the body although in many cases it seems to limit its expression predominantly to those organs and tissues supplied by the autonomic nervous system

The Unconscious — Parents unaware of the serious effects of trauma and deprivation in the life of the child may permit much psychopathology in the form of anxiety to develop in the first year of life Unwanted children are neglected often and fed carelessly as to rhythm or improperly as to the type of food or

exists One might go further to say that man has four ages first, his *chronological age* second his *physical age* third, his *intellectual age* and fourth, his *emotional age* For example one easily can think of an adult, who is chronologically forty physically fifty intellectually twelve and emotionally only five And it might be said that, if these various ages are in harmony, he is apt to be well and if they are in disharmony he is apt to be ill Such persons and the world is full of them furnish the soil for the development of psychosomatic illness Psychotherapy is a process which aims to bring about reeducation of the emotions and the psychosomatic approach takes cognizance of all factors, physical intellectual and emotional

It is not unusual for physicians to recommend pregnancy and parenthood as a cure for neurotic illness, instability in the husband or threatened divorce or separation This prescription is rarely if ever of value It is a pretty safe rule that the unstable person will not be helped by becoming a parent but usually will be made worse as a result of the added responsibility How often upon taking the history of neurotic persons, and especially women do we hear 'I was perfectly well until my first child was born, I haven t had a well day since' It is true that some neurotic women will feel better during pregnancy but they pay dearly for their short period of improvement Nor should the cost to the child be forgotten Not only does parenthood not cure neurosis but it prepares the way for another spoiled life because this is surely one of the ways in which neurosis is perpetuated The atmosphere of the home in which there is serious emotional maladjustment creates *the culture medium for the development* of further emotional problems This is the real social disease The advice to an incompatible couple What you need is a child — then you will have a common interest , is as unenlightened as it is dangerous While it may succeed in holding the marriage together, who can say how many children thus are sacrificed on the altar of incompatibility

Pregnancy, like marriage is an excellent institution and undoubtedly will persist but it is not to be recommended for therapeutic reasons My feeling is that we must reverse the process of recommending parenthood for emotional maladjustment and instead advise birth control until there is adequate emotional development for rearing a child

What has just been said suggests that there is such a thing as psychological infection and that the atmosphere of the home is the source of contagion

The Role of Anxiety — The central problem of disturbances of emotional origin is anxiety One cannot be well oriented in the field of psychiatry or psychosomatic medicine without considerable knowledge of the role of anxiety in the development of illness of emotional origin It lies at the root of all psychopathology and for that matter plays an important part in normal behavior The human being from birth onward has a need for optimum conditions of comfort

expression of the psychological conflict. Thus nervous vomiting may have disgust as one of its meanings. A more severe degree of organ neurosis or what is sometimes referred to as a *vegetative neurosis is a disorder in which actual* physical changes take place as a result of a profound psychological disturbance. Cardiospasm is an example. Just as psychosis probably represents in the mental sphere earlier and more serious emotional traumatic experience than neurosis, so does vegetative neurosis represent earlier and more profound psychological disturbance than conversion hysteria so far as psychosomatic medicine is concerned.

Relation of Symptoms to Life Situation. — There are certain epochs in life when psychosomatic affections are apt to make their appearance. These are outlined in Table I.

TABLE I

CORRELATION OF LIFE SITUATION AND SYMPTOM FORMATION

Oral Stage (first year of life)	
Food and love are being given to the child with no responsibilities exacted in return	Refusal to nurse, fretfulness when nursing, or overt or discontentment. Protest to weaning (crying or vomiting)
Anal Period (1–3 years)	
Responsibility of cleanliness and neatness has to be taken over in toilet habits and in other activities. This is not easy and the child needs much friendliness, understanding and patience to accomplish it without anxiety or detriment to personality development	Is toilet training accepted or is child stubbornly resistive, *wetting and soiling beyond* usual age of established cleanliness? Is there constipation, temper tantrum, stubbornness, resentment, destructiveness?
Genital Period (3–6 years)	
Period of increasing general and sexual curiosity. Period of beginning tender attachment to parent of opposite sex	Excessive masturbation, fretfulness, disobedience, aggression, cruelty, eneuresis, poor adjustment to the children
Latent Period (6–12 years)	
Period of primary education, identification with ideals and authority	How is social adjustment? Does he do well in studies? Does he mix well in classroom and playground? Is there sexual delinquency, truancy, aggressiveness, cruelty, poor sportsmanship, seclusiveness?
Puberty (12–15 years)	
Period of maturity and beginning activity of sex glands. Extra impetus given to entire emotional life, especially emotional patterns pertaining to love and sexuality	Are there anxiety attacks, fears of disease, of death, of harming others, nightmares, irritability, social anxiety, seclusiveness, loss of appetite, vomiting, diarrhea, cardiac palpitation?

From Weiss, E., and English, O. S.: Psychosomatic Medicine, p. 541 ... 1943

they are weaned forcibly and without regard for the limited adaptive powers of the infant to a new experience. Depending upon the constitution of the infant, such treatment is apt to cause anxiety. Memory impressions are made and psychological reflexes are built up. These patterns are "forgotten" with the passing of time, but if numerous or highly charged with anxiety, they may form the nucleus of illness later on. Very little of what happens to us is truly forgotten. Each event is registered on the brain as a memory with varying degrees of clearness, and what cannot be recalled is referred to as unconscious. That part of the mental mechanism which holds these memories and their accompanying charges of emotion, is called the *unconscious*, commonly referred to as the *unconscious mind*. The more pain, shame, disgust or other painful affect that occurs during development, the more likely that repression will occur and the more difficult it will be to recall the traumatic event in later life. The emotions combined with the memories and ideas accumulated during growth make the unconscious a dynamic center of psychic energy rather than a static storehouse of innocuous impressions.

Anxiety and the Gastrointestinal Tract. — The digestive processes form the most important phase of the child's life during the first year. If this function has been exposed to and associated with too much strife, deprivation or ill will, they become associated in the mind of the infant. One is "conditioned" to the other. The memories of unpleasant experiences associated with the gastrointestinal function exist in that part of the mind we call the unconscious. As the child grows older, life conditions often improve, *but a revival of the same situation* of deprivation at the hands of fate or ill will from classmates, business associates or spouse may reactivate anxiety. Now, if this anxiety and its cause are recognized and can be dealt with through escape, compromise or sharing with some stronger person the experiences and their effects, thus gaining reassurance and new strength, a solution is found. If the anxiety is not recognized and is not adequately discharged, it finds no release and must exert its force upon the body itself. Then some organ or organ system is very apt to bear the brunt of this potent force and will function badly as a result. If during the years when the swallowing and digestive processes are of paramount importance in the life of the child there were anxiety producing experiences, then similar experiences later in life are likely to reproduce symptoms of the upper gastrointestinal tract.

Organ Neurosis. — With regard to other related factors one may say that the earlier in life and the more profound the psychological traumatic experience, the more serious the resulting psychosomatic affection may prove to be. The term organ neurosis is used frequently to designate the disturbance in the working of a bodily organ resulting from psychic forces. But there are various degrees of organ neurosis. Perhaps the most simple expression of psychological conflict is the so-called conversion hysteria in which the symptom is the symbolic

TABLE II

NORMAL PERSONALITY		NEUROSES	PSYCHOSES
EMOTIONAL FEATURE			
Unhampered by mental conflict	Ability to reach a decision without too much stress or delay	Hampering mental conflicts Mild mood disturbances Capacity for decision impaired	Mental conflicts Severe mood disturbances Capacity for decision impaired
Satisfactory work capacity	Enjoys work No undue fatigue No need for frequent change Maintains optimum efficiency	Work not enjoyed Fatigue a frequent and pronounced symptom Impairment in work efficiency	Severe disturbances in efficiency, concentration upon or participation in work may be totally impossible
Ability to love someone other than self	Takes pleasure in social relationships, marital relationships, parental relationships. Can understand the emotional needs and point of view of others and make appropriate response	Disturbance in ability to enjoy social relations, i.e., inability to relate themselves to other in such a way as to gain security and emotional response. Limited capacity to give emotionally, yet some conventional relation to others is maintained even though imperfect and at the cost of anxiety	Severe disturbance in ability to relate themselves to others; in fact they tend to renounce their relation to others more or less completely
PHYSICAL STATE Absence of symptoms (of neurotic origin)		Conversion of emotional stress (anxiety) into somatic symptoms in one or many parts of body	Somatic symptom formation during onset of illness but eventually symptoms are in sphere of control of emotion, thought, speech, action Varying amount of loss in control of well integrated thought, emotion and speech, and regressions to childish levels—and/or solution of anxiety through false belief or false sensory perception

From Weiss, E. and English, O. S., Psychosomatic Medicine, p. 42

TABLE I—(*Continued*)

Adolescence (15–21 years) Period of secondary and college education Often the need to leave the home and live among strangers Beginning of love relationships Planning for life work career home marriage The fields of competition widen Conflicts over religion or ideals and current behavior	Are there symptoms occurring on leaving home on beginning or ending a love affair because of inability to compete? Are there seclusiveness and anxiety? A period in which the incidence of somatic symptoms is high[†]
Early Adult Life (21–40 years) Decisions must be made about love marriage work parenthood Parental support drops away after 21 if not before Responsibilities of adulthood are thrust upon one They catch up with one whether he is prepared for them or not May be stress of military service	Symptoms may appear in relation to engagement marriage pregnancy childbirth loss of job failure to adjust in marriage or new environment War neuroses
Middle Adult Life (40–60 years) Period when anticipated ambitions are lost or realized Children begin to leave home Women go through menopause Both sexes have to adjust to changing values	Women have to cope with the menopause and loss of companionship of the children May not be resourceful enough become depressed and anxious For men it is the age of business success and failure Of divorce Reactions to physical disease Cancerophobia depression and suicide
Late Adult Life and Old Age Period (60 years plus) Period of retirement for men forced or voluntary Dependency on children for support in both sexes Problems of physical disease (geriatrics) and the need for care by others	Symptoms of anxiety often appear after retirement and many symptoms are due to the frictions incident to living with children and in laws Arteriosclerosis and senile dementia usually make social adjustment more difficult

In the beginning of this discussion I suggested that there was no sharp line between normal and neurosis Nevertheless there are certain distinguishing features and indeed one of the first problems that presents itself to the physician in dealing with a patient is to try to determine whether one is dealing with a normal a neurotic or a psychotic personality Glover[5] has defined the normal personality as being (1) free of symptoms (2) unhampered by mental conflict (3) having a satisfactory working capacity and (4) being able to love someone other than oneself Neurosis and psychosis show pronounced deviations in each of these spheres as shown in Table II

woman's folder contained? Five and one half closely written pages of matter comprised under twenty-eight captions all neatly underlined with red ink and ruler! Figure out the time that probably took and then ask yourselves how much time and energy remained to devote to the clinical problem of that woman. We toil through those *five and one half pages in search of useful bits of information*. Here and there we find a few fragmentary and uncorrelated. In the place for social condition' it is stated that she is a widow under occupation that she is a housewife under marital history that she has four children but not a word about that fiasco of the eldest son. The paragraph on habits speaks of weight loss but gives no hint of the possible cause. Breathlessly we work down to the captions complaint onset of present illness and course of present illness and find only some sketchy references to pains in the back palpitation breathlessness on effort gas in the stomach and so on but never a word of the restaurant or the thoughts in the poor woman's head. Then comes the sacred array of paragraphs on the various systems with reiteration of shortness of breath under cardiorespiratory system of stomach gas under gastrointestinal etc etc

The writer of this history was evidently painstaking and industrious and yet what a mess he made of it. There is not the slightest doubt that if before he ever set foot in the medical school he had been confronted with this patient and had been asked to write down what he could find out about her condition he would have done incomparably better. And as a commentary on the teaching of clinical history taking is not that the height of irony? The reason for this enormity is obvious. The writer of the history has been so occupied in constructing and polishing the frame in order to meet the standard specifications that he has been unable to paint the picture indeed he has scarcely seen the patient and her experiences at all.

This case to be sure is worse than many of our hospital clinical histories but it is none the less a good illustration of a valid general criticism of unrestrained standardization namely stereotypism perfunctoriness mediocrity

( ) After a medical history which takes account of personal factors as well as medical facts we should make a complete physical examination and such laboratory tests as are necessary to exclude physical disease or to establish the precise nature of the organic problem and the amount of disability which it in itself is capable of causing

(3) Having assured the patient that no physical disease is present in the first instance or that it is present to a certain extent in the second group but that the disability is out of proportion to the disease it is usually easy by examples of psychic causes for such physiological disturbances as blushing gooseflesh palpitation and diarrhea to make the patient understand that a disturbance in his emotional life may be responsible for the symptoms

(4) Then important clues for this disturbance usually can be found by en

PSYCHOSOMATIC STUDY IN ILLNESS

In a general way it may be stated that in addition to the physical study the psychosomatic approach consists in getting to know the patient as a human being rather than as a mere medical case Too often as already stated the patient is looked upon as only a physiological mechanism and is studied by means of medical history and physical examination aided by ' instruments of precision and chemical tests Tape measure and test tubes carry the erroneous notion of exactness and thoroughness erroneous because the emotional life of the individual, which may hold the key to the solution of the problem is not investigated or at best inadequately so

While the subject cannot be discussed in detail usually the best procedure in dealing with these patients is as follows

(1) To satisfy ourselves and establish their confidence a thorough medical history should be taken this must contain more information regarding the family and social background of the patient than most of our present histories do Many years ago Kilgore[6] criticized the standardization of hospital clinical records His criticism part of which follows still stands The amazing epidemic of standardization that has been visited upon American institutions in this century has not permitted our clinical records to escape In practically all hospitals with any pretensions one finds the clinical records usually in trim aluminum covers with some variation in charts and laboratory sheets but with the clinical history proper invariably displayed under a stereotyped system of paragraphs with or without the guidance of printed forms The histories thereby are given an orderliness which is pleasing to the eye, and which makes a tacit claim to the admirable quality of thoroughness

And yet these standardized histories are open to a very serious criticism My criticism may be interpreted from the following illustration In a medical ward of a class A teaching hospital I recently saw a Jewess aged forty five years Five minutes conversation brought out the facts that she had always been in reasonably good health until after the death of her husband a year ago that she then looked hopefully for support from her eldest son but that about three months ago she gradually experienced the final and crushing conviction that his talents were limited to the selling of newspapers which yielded a profit of less than a dollar a day She therefore in addition to caring for her home and the younger children took employment in a restaurant, standing eight hours a day washing dishes Then came backache, sleepless nights of worry anorexia loss of 20 pounds nervousness utter exhaustion hospitalization Cursory examination revealed only the ordinary effects of such a life including possibly some thyroid disturbance

"Now I ask of you sticklers for form and order, what do you suppose that

very distressing to the patient and usually are not volunteered When the patient is assured that it is his feelings which are involved and not his mind and that the reason his memory fails him is because he is so preoccupied with concern over his problems then he may confess his fear that he was losing his mind or his ideas of doing away with himself

Once these ideas are brought to the surface and ventilated and the patient receives sufficient reassurance, then often much improvement occurs Indeed the intensity of the fear and the amount of reassurance necessary to abolish it serve as a crude index to the depth of the neurosis

The Anxiety Attack

Quite frequently the first pronounced evidence of neurosis may be an anxiety attack and again and again in studying the histories of patients with chronic invalidism of emotional origin we find that the first outspoken manifestation of illness was the sudden onset of anxiety with apprehension and dread There is a feeling of weakness, sweating and a sensation that something terrible is about to happen There is dyspnea palpitation and sometimes nausea The attacks usually last only a few minutes and subside rather quickly but may last for an hour or more Weakness and fatigue follow The emotional as well as the physical distress is so marked as to cause the patient to conclude that some very serious physical disability is present Almost never does he conclude that his difficulty is emotional Most people prefer to think that physical distress means physical disease and unfortunately physicians too frequently have assisted them in this belief When a patient with an acute anxiety attack is first examined the physician notes the rapid pulse and listens to the pounding heart and all too often permits the patient to believe that the heart is diseased that hyperthyroidism is present or covers his unwillingness to make a diagnosis of a psychological disorder by using some such term as neurocirculatory asthenia or autonomic imbalance This is immediately reassuring but ultimately harmful Sedatives are of very little help if the anxiety is acute sedation does not occur until the attack has spent itself anyhow To be consistent one gives no treatment other than personal reassurance To give drugs and do nothing about fear is to mislead the patient into feeling that his distress is due to altered physical pathology rather than to psychopathology

In treating the personality for the factors which produce anxiety we must realize that the patient is apt to be an elusive disinterested individual who once over the first attack does not want anyone to probe his feelings When he begins to have frequent attacks and is afraid to go where the attack may occur street subway stores etc he has regressed to a position in relation to his family which unconsciously he wishes to maintain Hence the cooperation

couraging a discussion of problems centering around vocational religious, marital and parent child relationships Usually this is best accomplished indirectly rather than by direct questions The more one can persuade such a patient to talk about his other troubles' the sooner do we come to an understanding of the ' present troubles The greater our success in switching the conversation from symptoms to personal affairs, the sooner do we come into possession of the real problem disturbing the patient We are all familiar with the patient, who is preoccupied with his bowel function and wants to talk about nothing else whose whole life really seems to surround his daily bowel movement It is the physician s duty tactfully to switch him from a discussion of his symptoms to a discussion of his personal life Encourage him to talk about himself as a person rather than as a medical case In adults domestic problems and professional and business relationships play a large part in functional illness In young unmarried people family relationships, choice of a career and often religious and sexual problems are important topics for discussion

Usually one or more of three special fears are uppermost in the minds of such patients One of the most common is fear of cancer, cancerphobia A great many patients think they have cancer, and indeed most women who consult physicians will have the idea at some time They do not always express it in fact, they rarely directly express their cancer fears They often disguise it by a complaint about a lump a swelling or a curious sensation in the abdomen or breast and when they are assured at the end of a complete physical examination that they are free from organic disease they heave a sigh of relief and say Oh, I am so glad because I thought I might have a cancer' With all of the propaganda for the early detection of cancer these fears are exaggerated and I presume it is the price that we must pay for instructing people about cancer I am not of course advising against such instruction it is only that we must realize that we add to the apprehension of many patients by our emphasis upon the early detection of cancer

Another common fear as already suggested is the fear of heart disease When pain in the precordial region as well as rapid beating of the heart, breathlessness and fatigue occur suspicion of heart disease often arises If we remember that the pain of cardiac neurosis bears no definite relationship to effort is frequently described as sticking needle like or soreness that often it is associated with inframammary tenderness and hyperalgesia so that the pressure of the stethoscope sometimes elicits it, and that it may be accompanied by a sense of choking as well as sighing respirations we will have no difficulty in the differential diagnosis particularly when we associate these symptoms with the whole picture and life situation of the individual with cardiac neurosis

(5) The inability to concentrate often gives rise to the fear of losing the mind' Along with this fear frequently there are ideas of suicide Both are

gastrointestinal tract is above all other systems the pathway through which emotions are often expressed in behavior Why this is so becomes apparent in the study of psychopathology

The whole approach can be summed up in the following fashion Understanding illness and treating sick people consist of something more than a knowledge of disease they necessitate looking upon illness as an aspect of behavior It means that the nature of bodily disorders can be appreciated only when emotional factors are investigated in addition to physical factors Such an approach can be applied to a wide variety of ailments and can be utilized very generally in talking with patients Nor does it require a very high degree of intelligence on the part of the patient to follow this simple explanation Patients in the clinic as well as those in private care can be dealt with in this fashion they are just as susceptible to these psychosomatic disorders

Sexual Factors

This again is a subject that cannot be treated in detail but one point of importance does deserve consideration at this juncture and that is the relation of sexuality to neuroses

Ever since the introduction of the epoch making studies of Freud to the problems of neurosis medicine has misunderstood his conception of sexuality He has been quoted often to the effect that disturbances in genital activity are the sole causes of the neuroses This is very far from the truth It is rather that difficulty in the sexual sphere appears as a revealing index to a neurotic personality and can be looked upon in that light In other words in much the same manner that urea retention serves as an index to an impending uremia so do disturbances in the sexual life of the individual such as varying degrees of frigidity in the female and varying degrees of impotence in the male serve as a reliable index to the kind of personality that is very apt to develop a neurosis Sexual difficulties are rarely in themselves the cause of the kind of the illness under consideration when they are important and the patient has a satisfactory relationship to the physician sufficient confidence will be gained eventually to permit discussion of these intimate matters In women questions regarding menstruation and child bearing often will lead naturally to such a discussion

In this connection let me suggest a cautious attitude in regard to marital maladjustments which are often in the background of obscure illnesses The better these problems are understood from the standpoint of personality study the clearer it becomes that serious emotional maladjustment is behind the marital problem Consequently casually to give advice regarding marriage and child bearing divorce and extramarital relationships as short cuts to involved emotional problems is to assume knowledge beyond present human understanding

of the family is necessary to make him come to his physician where he can be apprised of his real troubles and learn to correct them

Organ Language

A method of helping patients to understand their symptoms, which I find useful is based upon the symbolism of symptoms Patients are told that if they cannot find an outlet for tension of emotional origin by word or action the body will find a means of expressing this tension through a kind of 'organ language The psychopathology responsible for organ language cannot be discussed in detail but many clinical instances can be cited

For example, if a patient cannot swallow satisfactorily and no organic cause can be found it may mean there is something in the life situation of the patient that he "cannot swallow Nausea in the absence of organic disease sometimes means that the patient cannot stomach" this or that environmental factor Frequently a feeling of oppression in the chest accompanied by sighing respirations again in the absence of organic findings indicates that the patient has a "load on his chest' that he would like to get rid of by talking about his problems The patient who has lost his appetite and as a consequence has become severely undernourished so-called anorexia nervosa", which in its minor manifestations is such a common problem is very often emotionally starved before he becomes physically starved When he learns to taste life he will begin to taste food The common symptom, fatigue, very often is due to emotional conflict which uses up so much energy that little is left for other purposes Again emotional tension of unconscious origin frequently expresses itself as muscle tension giving rise to aches and pains and sometimes these are represented by sharp pains such as atypical neuralgia Thus we suggest that atypical neuralgia of the arm or face may be due to focal conflict as well as focal infection An ache in the arm instead of representing the response to a focus of infection may mean that the patient would like to strike someone but is prevented from doing so by the affection or respect that is mingled with his hostility Itching for which no physical cause is found, very often represents dissatisfaction with the environment which the individual takes out upon himself martyr like he scratches himself instead of someone else ' All gone feelings in the epigastrium ' shaky legs and even vertigo are common physical expressions of anxiety, and the anxiety attack so frequently called a heart attack, a gall bladder disturbance hyperthyroidism neurocirculatory asthenia hyperinsulinism, etc , is still far from being understood in general clinical medicine in spite of the fact that Freud[7] described it more than forty years ago

Many more examples could be given but are unnecessary Only one more point remains before concluding this part of the discussion, and that is that the

Between simple reassurance at one end of the scale and adequate psychoanalysis at the other there are all degrees of psychotherapy which can be applied depending upon the degree of illness and the circumstances of the patient

It is my hope that every physician will be trained in psychological medicine so that he may be able to understand and manage the many emotional problems that are presented to him daily It is possible that some internists will wish to perfect themselves in psychosomatic medicine in the same way that others interest themselves chiefly in cardiology gastroenterology and other fields Certainly better training facilities should be developed for residents in medicine to acquire the psychosomatic approach to medical problems At the same time an opportunity for residents in psychiatry to have more medical training would do a great deal to break down the false alignment between psychiatry and medicine It would provide us with capable teachers who could cooperate in giving medical students the psychosomatic point of view Therein lies our hope for an important development in medicine As a part of this process and essential for its development general hospitals must establish divisions for the observation and treatment of psychoneurotic and psychosomatic problems The time has passed for psychiatry to lead an isolated existence Until it is brought into physical proximity with general medicine it cannot achieve final integration into the body of medical knowledge

Major and Minor Psychotherapy

A considerable number of the patients whom we have been considering cannot be sent to psychiatrists nor is it necessary Not that there is anything reprehensible about consulting a psychiatrist this too is a problem of education but there are not enough psychiatrists to take care of the thousands of patients and moreover as I have tried to show a great part of this work lies in the field of general medicine Another way of stating the problem is to say that there is a major and a minor psychotherapy just as there is a major and a minor surgery Many physicians who practice general medicine feel themselves capable of doing minor surgery but only a few have the skill to attempt major surgery They would not permit themselves to attempt something for which they are not prepared This is just as true in regard to psychotherapy The general physician must be able to treat the minor ailments but he must be able also to recognize when the problem is beyond him and then refer the patient elsewhere for major psychotherapy Such knowledge and such an approach frequently will save the patient from unnecessary troublesome and expensive medical or surgical treatment with a resulting further degree of invalidism So much for some of the more obvious benefits to be achieved by the psychosomatic approach But as a part of what is intended as a practical introduction to psychosomatic medicine a word must be said about the cost of psychotherapy

PSYCHOTHERAPY

And now to come to a question frequently raised regarding these matters "Suppose you do find something of importance in the emotional life of a patient some conflict that is causing illness, What good does it do the patient to know? What can you do about it?'

First of all, it is often a great help to the patient to know that the ailment is not organic but is due to a disturbance in his emotional life When a neurotic symptom is divorced from a fear of organic disease cancer for example it loses its force, whereupon the slogan "carry on in spite of symptoms often helps the patient a great deal This is especially true if the psychological approach which we have discussed, is a part of the study and the emotional background of the illness is made clear to the patient

What Is Psychotherapy?

What indeed is psychotherapy? Too often it is assumed to be something vaguely referred to as "the application of the art of medicine' This defies analysis but seems to represent a combination of the experience and common sense of the seasoned practitioner an intuitive knowledge of people the cultivation of a charming bedside manner, such trifles as serving food in attractive dishes and the generous use of reassurance The psychological approach in medicine essential for psychotherapy, consists of something more It is a medical discipline to an equal degree with internal medicine itself It is an effort to understand the personality structure of patients the mental mechanisms which are at work and the specific relationships of psychological situations in the precipitation of the illness

Reassurance in the majority of instances unless combined with an analysis of the illness from the standpoint of the behavior, gives only temporary help and depending upon the degree of anxiety has to be repeated constantly, like a dose of digitalis in a failing heart Closely allied to reassurance is another superficial treatment that rarely results in more than temporary help, i e, environmental manipulation without any attempt to give the patient insight into his conflicts

Real psychotherapy, which is directly the opposite of simple reassurance tries to make the patient understand the meaning of his symptoms and the nature of his conflicts It is a process of reeducation and when properly done, leads to sufficient emotional development so that the necessity for symptom formation is abolished The best example of this kind of psychotherapy is psychoanalysis but for various reasons this method cannot be applied directly to the majority of patients Nevertheless psychoanalytic insight and guidance prove adequate to handle the emotional factor in the majority of psychosomatic disturbances

tion of disease Yet there is nothing new or startling in this viewpoint We have heard a great deal in recent years about the study of the organism as a whole but for most part we have been paying only lip service to this concept We have been led to believe that the art of the physician having to do with his common sense or intuition as opposed to his science is sufficient to grasp the problems that we have been considering It is not enough A real understanding of psychopathology is necessary in order to study the emotional life in relation to ill health In other words the physician must be able to define the specif mental factors producing the illness rather than to be satisfied with vague generalizations about neurogenic background Just as we would criticize the physician of today who would call all fevers malaria so we must criticize the physician of tomorrow who hints vaguely at nervous factors in the background of an illness and makes no effort really to understand the psychic situation

In his History of Medicine Garrison states that the fundamental error of medieval medical science as originally pointed out by Guy de Chauliac and elucidated by Allbutt was in the divorce of medicine from surgery He might have added that the fundamental error of modern medical science has been in the divorce of both from psychiatry

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Cost of Psychotherapy

What about the question of time effort and the expense of psychotherapy? True it is that all of this takes time and effort and must be paid for, yet when we look into the time, effort and expense that have been expended by many patients or by institutions taking care of these patients in the usual medical approach we realize that an hour or two well spent in a discussion of the life situation of such patients would obviate a great deal of this expense It is amazing what the total expense of a great many of these unnecessary studies amounts to so far as the institution is concerned, and of course the same thing is true in the case of private patients The day is close at hand when we will regard some of these thick chart patients this polyphysical approach, with the same amusement and disdain with which we now regard the polypharmacy of a bygone age *in medicine Hospitals are beginning to understand that it is not only intelligent* but economical to utilize the service of a psychiatrist in the general medical division and this same idea could be applied with great benefit to the much discussed medical insurance plans To quote Dunbar[8] on this subject Although the psychic factor is more regularly overlooked in the case of severe somatic damage , and in the handling of convalescence and chronic illness it is no less important in our failures — patients who wander from physician to physician and clinic to clinic If a patient has received treatment from a dozen or two private physicians and half a dozen clinics and has submitted to elaborate and expensive laboratory procedures in each place one may be justified *in suspecting* that his physicians have in some way failed to find out what was the matter Usually when this happens it is because a prominent psychic factor is present Such patients are a real drain on hospital and clinic time and funds They can be effectively treated only if equal attention is given to the psychic and somatic aspects of their illness

There is need of an adequate basis for the inclusion of attention to the psychic component in illness in our public health program Its inclusion is exigent both because of the facts just stated and in view of the problems of health insurance and *socialized medicine* with which we are confronted *A major* weakness of such systems as are in operation results from a lack of knowledge concerning emotions and physiological changes It is chronic illness as well as those illnesses which have the greatest tendency to become chronic in which the psychic component is of the greatest significance to therapy

Summary

The main point of this discussion can be stated briefly, the study and treatment of illness constitutes much more than the investigation and eradica

CHAPTER XXI

PHYSICAL MEDICINE

By FRANK H. KRUSEN

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LOCAL APPLICATION OF HEAT

The application of heat locally is one of the most common procedures in the practice of medicine Heat may be applied by conduction convection or conversion The application of conductive heat by direct application of water is discussed later in the section on *Hydrotherapy* The procedures for applying conversive heat locally are described in the section on *Electrotherapy* The majority of the methods of applying conductive heat and the procedure for application of convective heat are considered here

Conductive heating can be accomplished by the direct application of a warm object to a bodily surface Conductive heating devices can be heated by means of (1) warm air (2) warm water (3) chemicals or (4) electrical resistance coils Previously heated solids or semisolids also can be employed for conductive heating

Convective heating usually is accomplished by reflection of infra red or luminous radiant energy on some region of the body

METHOD OF APPLYING HEAT LOCALLY

Conductive Heat

Warm Air Devices — Hot air chambers blowers or applicators heated from within by means of hot air have been used medically Hot air chambers (Fig 1) constructed of wood or metal and lined with asbestos were developed by August Bier[1] and described by Willy Meyer more than forty years ago Although such chambers have been abandoned to a large extent in this country they still are employed enthusiastically by South American and Italian physicians The chambers have an opening at one end to permit the insertion of an arm or leg Usually they are heated by an alcohol lamp or by a can of solidified alcohol The air within the chamber usually is extremely hot attaining a temperature of 250° to 260 F (121° to 125° C)

Recently the Council on Physical Therapy of the American Medical Association approved a device which circulates warm air within a sleeve fastened to an extremity An apparatus which circulates hot air within a distensible rubber bag also is being recommended currently The bag is inserted into the vagina for treatment of pelvic inflammatory disease The pressure usually is 1 to 1½ pounds (0 5 to 0 7 kg) and the temperature not more than 130 F (54 4° C)[2]

Warm Water Devices — The time honored hot water bottle falls in

usual cap Its purpose is to maintain the temperature of the water within the bag at a constant level

The Elliott apparatus heats and circulates water which is passed under pressure through thin rubber applicators These applicators are constructed for insertion into various bodily orifices

Chemical Devices — Pads which make use of the latent heat of crystallization to produce prolonged heating effects have been employed therapeutically These pads have been constructed for application to the eye[4] to the frontal region[5] or to other regions of the body[6] One type[4, 5] of chemical heating pad contains sodium acetate 90 5 per cent glycerin 3 per cent sodium sulfate crystals 2 per cent and anhydrous sodium sulfate 4 5 per cent These chemicals are sealed inside the rubber applicator which is boiled for ten minutes before use The pad then will remain at a temperature of about 108° to 114° F (42 2° to 45 5 C) for approximately an hour It has a lifetime of about 600 hours of service

The other type of chemical heating pad[6] depend on the chemical reaction which occurs when water is added to a mixture of finely divided iron 84 per cent sodium chloride 6 per cent and manganese dioxide 10 per cent The chemicals are placed in a canvas bag enclosed in flexible rubber If 2 drachms (7 5 c c) of water are placed inside the container heat will be liberated After use if the cover is removed it will cool rapidly It has a useful life of 80 to 125 hours

Devices Containing Electrical Resistance Coils — Pads containing electrical resistance coils with a flexible insulated covering are used commonly today In fact they have become household utility devices Such pads are not satisfactory for therapy They tend to become too hot temperature control is inadequate and the fact that they produce burns or shocks occasionally is reported

Electrical pads which can be controlled more accurately than the household heating pad have been constructed for therapeutic use One such device[7] consists of a flat coil contained in a waterproof cover A thermostat of considerable accuracy permits minute adjustments of temperature A mercury thermometer inserted in a pocket in the cover allows close observation of the temperature The pad is intended to be used for the purpose of keeping hot moist dressings at a constant temperature

Parts of an electrically heated suit similar to those worn by deep sea divers and stratosphere fliers have been employed therapeutically for local application of heat to a certain region of the body Brown and Allen[8] used cuffs or sleeves of this sort in treatment of peripheral vascular diseases Recently I have had constructed a device of this type for appli

this category as does the so called Elliott treatment regulator The hot water bottle is sufficiently well known to preclude the necessity of careful

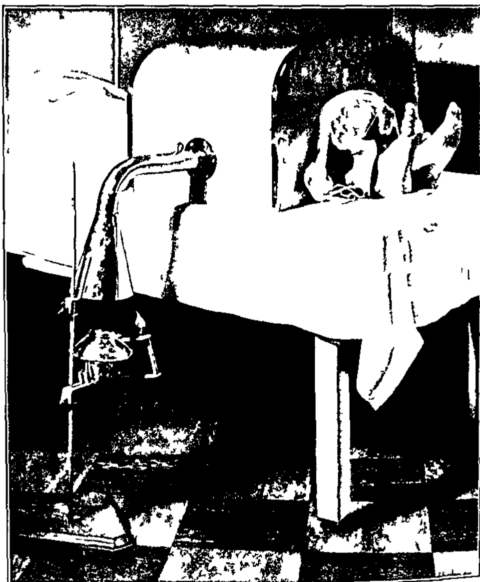


Fig 1 A hot air chamber for local application of heat Although still employed enthusiastically in some parts of the world in the United States this device now has become almost obsolete

description Recently an electrical immersion heater has been developed which can be inserted in the standard hot water bottle in place of the

during cold weather Likewise it should be valuable in providing a safe type of warm bed to combat postoperative surgical shock There would not be the danger which has been observed so often in the past of burning semiconscious patients with hot water bottles

Previously Heated Solids and Semisolids — The ancient household custom of applying hot irons hot bricks hot salt bags or hot sand bags to various regions of the body for relief of pain or of muscular spasm has declined recently This is largely because of the fact that the temperature

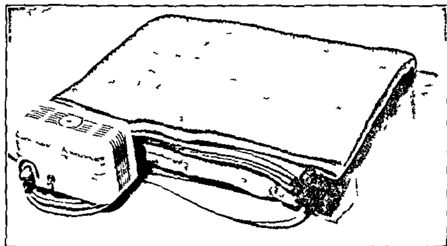


Fig 3 An automatic electric blanket the temperature of which can be adjusted to the desired level This temperature is maintained by means of a thermostat despite changes in environmental temperature (From Krusen F H Physical Medicine Saunders Philadelphia 1941)

of the simple devices of a similar nature which are now readily available can be controlled more accurately

The employment of hot mud packs has been popularized commercially by certain European spas The claims for alleged specific effects of various types of therapeutic muds have been vague and completely unconvincing Typical examples of this kind of supposedly therapeutic mud are the piestany mud and the fango mud There is no convincing evidence that such muds contain constituents which enhance their effectiveness when they are applied to the surface of the body

Working in my department R L Bennett checked the action on photographic paper of the allegedly radioactive fango mud He found that there was insufficient radioactivity to fog the paper even after exposure for twenty four hours It was concluded that the supposed

cation of conductive heat to the shoulder and upper part of the arm (Fig 2) It has the advantage of providing uniform heating of all the surfaces of the shoulder and arm surrounded by it All or any part of an electrically heated suit thus can be constructed so that regulated conductive heat can be applied to all sides of various regions of the body

Recently an ingenious electric blanket (Fig 3) has been developed this was intended primarily for household employment but may be found extremely useful in medical practice[9] A transformer within the control



Fig 2 A new type of electrically heated shoulder and arm pad with an accurate thermostatic control It has the advantage of providing uniform heating of all surfaces

box reduces the usual 115 volt current to 18 volts at the blanket This practically eliminates the danger of electrical shock A thermostat in the control box can be adjusted manually to the desired level of temperature It then will maintain this level despite changes in the temperature of the room If the environmental temperature rises the blanket will cool and conversely if the room becomes cool the blanket will warm up until the predetermined level is reached

This type of blanket should prove valuable for maintenance of a constant optimal bodily temperature in certain cases of peripheral vascular disease It might prove valuable also for keeping tuberculous patients at a constant comfortable warmth while sleeping in well ventilated rooms

A variety of infra red generators has been marketed for therapeutic use. The units commonly employed at present consist of a spiral coil of resistant metal wire wound around a cone made of steatite or porcelain or plates, rods or disks of resistant metal such as carborundum. These units usually are placed in a cup-shaped reflector which will cause the rays to converge on the part which is to be treated (Fig 4). The infra red lamp

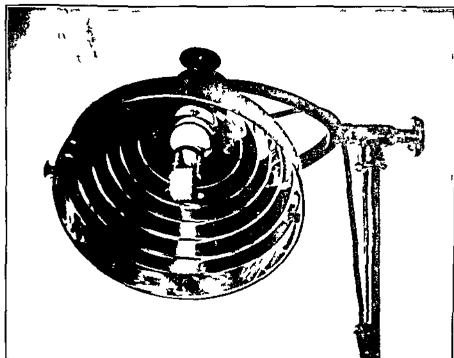


FIG 4. An infra red unit (nonluminous variety) in the usual type of cup-shaped reflector which causes the radiation to converge to a focal point.

employed by the physician differs little from the familiar household electric heater (Fig 5). The chief difference is in the shape of the reflector. The household heater has a flatter platelike reflector which diffuses the heat rays through the room while the infra red lamp has a more concave cup-shaped reflector which concentrates the rays on a small local region. The heating units themselves can be used interchangeably because the radiation from one is practically identical with that from the other.

It is obvious therefore that infra red rays are not mysterious or unusual. However even though infra red rays simply are heat rays they

radioactivity would have a negligible therapeutic effect. In addition comparative clinical tests were performed which revealed no essential differences between the thermal effects of "Fango" mud, ordinary garden mud and Mississippi valley clay. It would seem that "therapeutic" muds have no particular advantage over simpler and cleaner methods of applying heat.

Hot paraffin can be applied easily to local regions and is clean and effective. All the materials which are necessary are jelly wax or ordinary commercial paraffin, a kitchen stove and a double boiler such as can be found in any kitchen. I frequently recommend that paraffin be employed for local application of heat when the patient lives in a house which is not equipped with electricity to operate a homemade baker or a simple heat lamp. But even in well supplied institutions paraffin frequently is employed *in preference to other local heating measures*. The paraffin is placed in the inner pan of the double boiler and water is poured into the outer pan. The boiler then is placed on the stove and heated until all the paraffin has melted. It is permitted then to cool until a thin film of solidifying paraffin has formed on the surface. At this time the paraffin will be at its low melting point which is approximately 167° to 176° F (75° to 80° C).

The paraffin then is painted over the region which is to be treated. About a dozen coats are applied in rapid succession. The layers of paraffin solidify almost instantly to form a thick warm covering of the surface. This covering is left in place for at least thirty minutes. Variations include dipping of a part, usually a hand or foot, in the paraffin about six times to form a similar warm paraffin pack, applying alternate layers of bandage and paraffin to a joint to provide a warm firm supporting dressing, or leaving the part immersed in a special large paraffin bath for thirty minutes or longer.

I have placed thermocouples beneath paraffin packs or dressings and have found that the temperature is kept above normal levels for more than an hour.

Convective Heat

Convective heating is accomplished by irradiation of the surface of the body with rays from the visible and infra-red regions of the electromagnetic spectrum. A beam of visible light can be split by means of a triangular prism into the various colors of the rainbow. Above the violet end of this rainbow are situated the invisible ultraviolet rays; below the red end lie the invisible infra-red or heat rays.

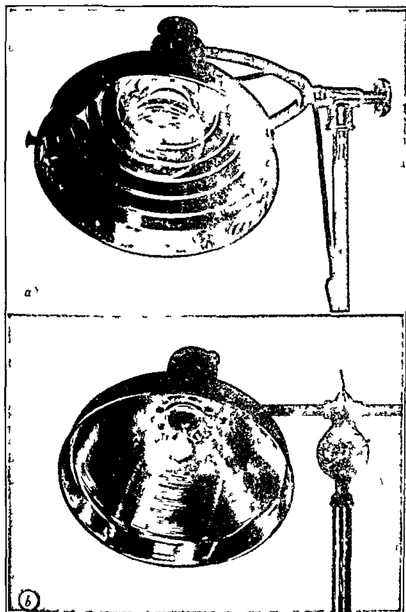


Fig 6 Luminous type of infra red unit in a suitable cup shaped reflector (a) a tungsten filament lamp (b) a carbon filament lamp

are nevertheless of considerable usefulness in therapy. For many years illumination engineers have known that radiation from luminous sources such as tungsten or carbon filament bulbs penetrates human tissues to a greater depth than that from nonluminous sources such as the infra red coils or plates. Oddly enough physicians have not been familiar as a rule with this fact. Somehow many physicians have entertained the erroneous idea that the radiation from infra red coils penetrates to great depths. Actually the rays from the far portion of the infra red spectrum which are produced by these nonluminous or black body radiators penetrate in appreciable amounts to a depth of less than 1 mm.

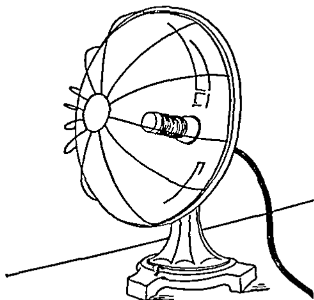


FIG 5 An ordinary household electrical heater. The heating unit produces radiation similar to that emitted by the therapeutic infra red unit but the flatter reflector tends to diffuse the radiation (From Krusen F H Light Therapy Ed 2 Hoeber New York 1937)

The greatest amount of penetration of convective heat can be obtained from luminous sources which produce considerable amounts of radiation in the near portion of the infra red spectrum such as carbon filament or tungsten filament lamps (Fig 6a and b). These infra red luminous bulbs can be placed in the same cup shaped reflectors which are employed for the nonluminous infra red coils. The penetration through human tissues of radiation from the luminous bulbs has been estimated variously up to depths of 1 5 cm. Recently however Hardy and Muschenheim[10] reported careful investigations which indicated that the transmission through skin of even these most penetrating infra red rays

ing near infra red rays but cuts off practically all of the visible rays and thus eliminates glare (Fig 7) This lamp seems to be especially valuable

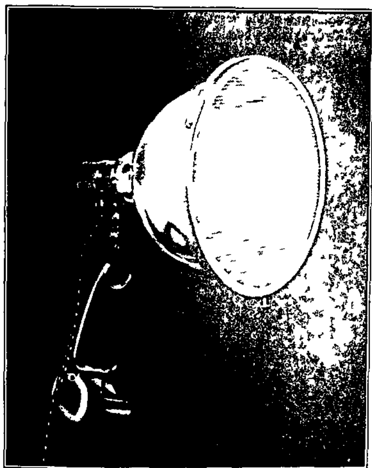


Fig 8 An inexpensive clamp lamp which can be employed at home for prolonged local heating of various regions of the body (From Krusen F H Physical therapy in arthritis with special reference to home treatment Jour Am Med Assoc 1940 CXV 605)

for application of heat to the face and to the upper anterior part of the body because the patient is not annoyed by glare

A strange phenomenon has been the development in this country of small inexpensive heat lamps consisting of a bulb on a small reflector attached to a handle It is undoubtedly of great usefulness to have inexpensive heat lamps readily available but the catch is that almost no

is slight They found that about 95 per cent of the rays were absorbed within 2 mm of the surface and 99 per cent within 3 mm

For most therapeutic applications it will be advisable to employ a source of radiation which is rich in the more penetrating near infra red rays Therefore convective heat treatments usually should be administered with a device which converges the rays from a luminous source on

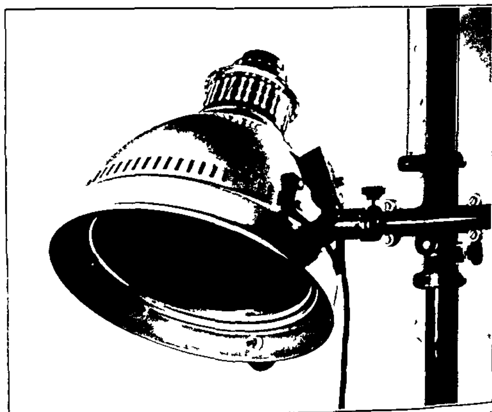


FIG 7 A radiant heat lamp luminous type of infra red bulb with a special black glass filter which eliminates glare but does transmit most of the more penetrating near infra red rays (From Krusen F H A new type of filter for efficient infra red radiation Proc Staff Meet Mayo Clin 1941 XIV 22)

the part to be treated For example one type of luminous therapeutic heat bulb which is known as the Mazda CX bulb is particularly rich in the slightly more penetrating near infra red rays Thirty per cent of the radiation from this type of bulb is within the most penetrating range with wavelengths between 770 and 1 200 millimicrons

One disadvantage of the high voltage heat bulb is that it produces considerable glare I recently have described[11] a new type of infra red lamp with a special black glass filter which transmits most of the penetrat

Still extremely serviceable is the old style baker which consists of a slightly curved rooflike reflector supported by adjustable legs Beneath this reflector are several small electric light bulbs This tunnel like heating device can be placed over a leg an arm or the back (Fig 9) A

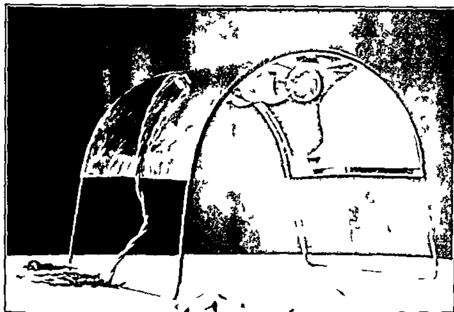


Fig 10 Inexpensive homemade baker Four bulbs are covered by a reflector of sheet tin on framework of iron rod

similar less elaborate baker for home use can be constructed of four light bulbs covered by a piece of polished sheet tin supported on a light framework of iron rods (Fig 10)

Physical Principles Concerned in the Local Application of Heat

Since heat is a form of irregular molecular motion thermal energy can be transmitted from one body to another by continuation of this molecular motion Interchanges of this sort are taking place continually between the human body and its environment As previously mentioned such transmission of molecular motion can take place by conduction convection or conversion

All of the conductive methods which have been described require direct application of the hot applicator to some surface of the body

body wishes to hold such a lamp steadily in his hand long enough for it to produce any marked therapeutic effect It usually requires at least thirty minutes of local application of heat to produce an effective increase in temperature of the tissues It is extremely tiresome even if the hands are shifted to hold a lamp steadily in one position for thirty minutes

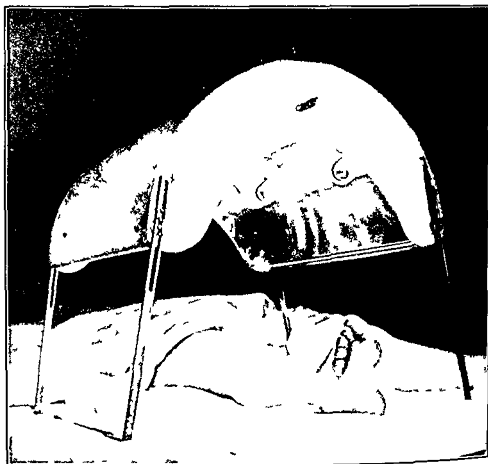


FIG 9 Institutional type of baker This is a luminous heat device containing usually four to twelve light bulbs

To obviate this difficulty I have had constructed an inexpensive clamp lamp which was described a few years ago[1] This lamp has a cup shaped reflector containing a luminous heat bulb Instead of a handle a clamp similar to that employed for photo flash lamps is provided This inexpensive clamp lamp can be attached to the side of a bed or to the back of a chair A ball and socket joint permits adjustment of the reflector at any angle The lamp can be employed easily for prolonged heating of various local regions of the body (Fig 8)

Local applications of heat will tend to raise the temperature in peripheral regions.

It is probable that bodily tissues cannot tolerate a *prolonged* increase of external temperature to more than 113 F (45° C) without being damaged. For *short periods* of time they can tolerate changes of external temperature exceeding 36 F (20° C) without evidence of injury. Local application of heat produces dilatation of blood vessels and an increase in the rate of flow of the blood. The tendency toward rapid dissemination of the heat finally may result in an increase in the systemic temperature. There is evidence that the heat causes increase of phagocytic and local metabolic activity. Heating of the blood increases carbon dioxide tension and acidity. *It has been suggested*[13] *that these changes may be of some* value in modifying the reactions of tissues to infection.

A point worth keeping in mind is that local exposure to infra-red radiation will produce a rise of temperature of a considerable volume of blood as it circulates through the cutaneous capillaries. The temperature of the blood will reach a level exceeding that of the average systemic fever without any appreciable rise in the systemic temperature. Local applications of heat possibly may stimulate intracellular oxidation. Likewise sweating and muscular relaxation are produced by local heating.

Daily treatments for thirty minutes in the hot air chambers and blowers have been recommended particularly as an adjunct in the management of various forms of arthritis. The vaginal applicator which is heated by circulating hot air usually is employed for sessions of one hour daily in treatment for specific and nonspecific inflammatory disease of the pelvis.

Like the hot air device the Elliott apparatus which circulates hot water through a distensible rubber bag within the vagina is employed chiefly for pelvic inflammatory disease. The water pressure meter should register 2 or 3 pounds (0.9 or 1.4 kg.). Hourly treatments usually are given once or twice a day. Randall and I[4] found that complete clinical remissions were obtained in 55 per cent of our 45 cases of chronic gonorrheal inflammatory disease of the pelvis in which treatment with the Elliott device was employed; in an additional 2.. per cent negative cultures developed but there was evidence of residual salpingo-oophoritis; in 11 per cent improvement did not occur and in 11 per cent insufficient treatment was received. Of our group of 173 patients suffering from nonspecific pelvic inflammatory disease 30 per cent were greatly improved after Elliott treatment, 27.7 per cent were moderately improved, 9.8 per cent were slightly improved and 5.7 per cent were unimproved. Surgical treatment was required in 26.5 per cent of the cases. Pelvic heating with

Luminous and infra red rays result from electromagnetic disturbances of the ether According to Huygens wave theory there is a propagation of energy in the form of waves Wavelength is the distance between the crests of adjoining ether waves

Because the frequency of vibration of a given source of heat energy is uniform and the velocity of the radiation is constant the distance between any two adjacent waves will be identical with the distance between any other two waves derived from the same source

The electromagnetic spectrum can be defined as a graphic representation of the various waves of energy in ascending order of length (Fig 11) Starting with the shortest known rays the cosmic rays it will be seen that the next shortest in ascending order are the gamma rays of radium Forming a continuous spectrum in succession of increasing wavelengths from these are the roentgen rays ultraviolet rays visible light infra red rays hertzian waves including the short and long radio waves and alternating current waves

Those portions of the spectrum which contain radiations employed for convective heating are the visible and infra red regions The wavelengths of the rays from this portion of the spectrum vary between 290 and 15 000 millimicrons

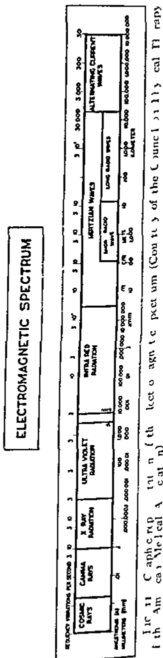


Fig 11 Graphic representation of the electromagnetic spectrum (Courtesy of the Council on Physical Therapy of the American Medical Association)

Action and Uses of Local Heating Devices

The action of conductive or conversive heating is superficial because the penetration of heat is always slight Normally the temperature of the blood in various peripheral regions of the body is lower than the central temperature of approximately 98 6 F (37° C) The temperature of the skin fat and muscle in peripheral regions varies and usually is considerably lower than the rectal temperature

massage will tend to promote absorption and to prevent the formation of organized hematomas

Traumatic synovitis tenosynovitis bursitis spastic muscles and strained muscles often can be benefited by local applications of conductive or convective heat

Contraindications to the Local Application of Heat

The great danger in applying any form of therapeutic heating is that burns may be caused Patients have been known to permit themselves to be burned thinking that they were supposed to tolerate the pain It is not sufficient to give the patient a bell and to tell him to ring it if the part becomes too hot I recall one patient who although he had been so instructed promptly permitted himself to be burned and then explained that he did not know how much too hot was Therefore the patient must be told that he should feel only comfortable warmth that the minute he feels the slightest discomfort he should ring He should be warned that excessive heat will do more harm than good

Heat always must be applied with extreme caution to extremities in which the circulation is impaired In the presence of peripheral vascular disease heat will be disseminated poorly by the impaired circulation therefore burns are more likely to occur Furthermore if a burn does result slowly healing lesions or even gangrene may occur in the devitalized tissue It should be remembered in dealing with peripheral vascular diseases that the local application of heat to an unaffected region may produce vasodilatation in the affected part Local heating of an uninvolved region may be just as effective as direct heating and it is much safer If heat is to be applied locally to the affected extremity prolonged applications at fairly low temperatures 91 4 to 95 F (33 to 35 C) are safer than short exposures at high temperature

Heat always must be applied with great caution over old scars which are comparatively avascular and will blister readily It often is wise to cover small scars in a region which is to be heated Likewise heat must be applied with extreme caution over anesthetic regions Because there is no sensation the patient may be burned without realizing it

Knapp[17] recently has expressed the opinion that in most instances just sufficient heat should be applied to produce a faint pink blush on the skin He concluded that if there was a mottled erythema of the skin the heat was too intense It seems obvious that the mottling so commonly observed during intense heating of the skin indicates unequal

the Elliott device was employed successfully to promote absorption of exudates following pelvic operation

The Elliott treatment has been applied through a rectal applicator for chronic prostatitis specific and nonspecific and a urethral applicator was employed by Emmett in treatment for nonspecific urethritis among females Welch and I have administered Elliott treatments through a colonic stoma to lessen edema of the spur and to permit earlier application of clamps for the second stage of the Mikulicz operation

The chemical heating pads have been employed chiefly for chronic inflammation of the eye or nasal accessory sinuses The larger chemical heating pad has been used as a substitute for the hot water bottle and has the advantage that it will remain hot for a longer period

Ordinary electrical heating pads should not be used unless more suitable methods of heating are not available The compress with accurate thermostatic control can be employed to maintain the warmth of wet dressings at proper level for infections acute inflammations cutaneous diseases and surgical conditions The electrically heated sleeves cuffs and pads which have accurate control can be employed for peripheral vascular diseases arthritis and traumatic lesions

Applications of hot paraffin have been recommended chiefly for contractures arthritis fibrositis post traumatic stiff joints and lacerations

The application of infra red radiation has been advocated for numerous conditions It tends to promote absorption of exudates because heat produces not a passive congestion but an active hyperemia with an increase in the volume of blood flowing through the region rather than engorgement and stagnation

Local treatment with infra red radiation has been recommended[15, 16] for various types of neuritis myositis fibrositis and arthritis for circulatory diseases for certain types of paralysis and also for traumatic lesions such as sprains contusions dislocations and fractures It always should be remembered that various conductive methods of applying heat often can be substituted for infra red radiation or vice versa The therapeutic effects are essentially the same The choice of the superficial heating agent will be largely a matter of convenience

Following trauma heat should not be applied until the danger of capillary oozing with extravasation and ecchymosis has ceased This usually will require twenty four to forty eight hours During this time tight dressings immobilization and applications of cold are in order As soon as this danger disappears applications of heat for periods of thirty minutes or longer once or twice a day should be begun After the applications of heat massage sometimes can be administered The heat and

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distribution of the hyperemia in the region under treatment Certainly it is safer to avoid the mottling when possible

Local exposures to heat may aggravate certain cutaneous rashes As a rule local heat should not be applied in febrile conditions Occasionally sensitivity to heat attributable usually to derangement of the heat regulating mechanism may be encountered In such instances local heating must be applied with great caution

When Elliott treatments are administered to the vagina incorrect placing or improper distention of the applicator may produce excessive localization of heat in a small region and severe burns may ensue Large sloughs of the anterior vaginal wall have been reported after incorrect employment of the procedure

If hot paraffin is used for local heating, in rare instances a mild paraffin rash may be produced

Summary of Data on Local Heat

There are numerous readily available sources of heat which can be employed in local treatment for various diseases Devices heated by warm air warm water chemicals electrical coils previously heated solids and semisolids and several sources of infra red radiation can be used

These devices are employed chiefly to increase local temperature and circulation to increase local metabolism to promote absorption and to relieve muscular spasm *Local applications of heat are indicated* especially in the management of acute and chronic inflammations impairment of circulation and various traumatic lesions Heat should be applied with great caution in the presence of peripheral vascular disease scars or anesthesia of the skin

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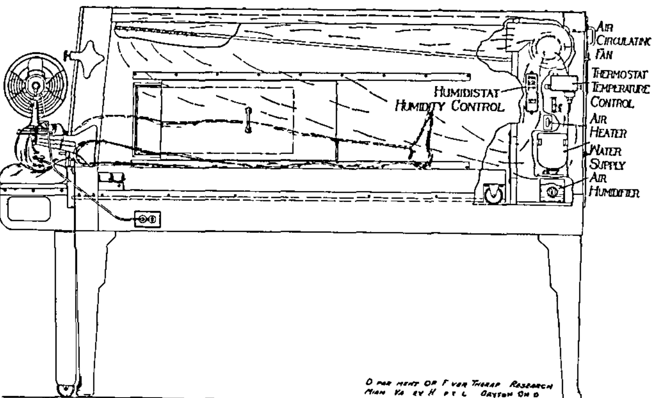


FIG 1 Plan of the hot humid air fever cabinet (Kettering hypertherm) (Courtesy of Dr Walter M Simpson)

GENERAL APPLICATION OF HEAT

The general or systemic heating of the human body for therapeutic purposes now is spoken of commonly as "fever therapy." There are several methods of obtaining increases in bodily temperature by physical means and recently much interest has developed in the employment of these devices for the production of artificial fevers.

A few decades ago fever was considered by physicians to be a manifestation of disease which should be combated. Therefore much of the internal medication, chiefly with the derivatives of coal tar, was directed toward abolishing fevers. At present it is believed that spontaneous fever often is an indication of the benign efforts of nature to overcome disease. Today in certain types of disease in which spontaneous fever does not occur the physician makes a therapeutic effort to produce a fever by physical or other means.

Recently much fundamental and clinical research has been done in this field. Fever therapy, at least when high temperatures are used, now is considered a major procedure which should be employed only in well equipped institutions possessing skilled personnel. The procedure seems logical and appears to have far reaching possibilities.

METHODS OF PRODUCING GENERAL HEATING OF THE BODY (FEVER THERAPY)

Rises in systemic temperature can be produced physically by the use of (1) cabinets within which circulates hot humid air, (2) cabinets heated by luminous heat bulbs or nonluminous heating coils, (3) diathermy, (4) hot tub or spray baths or (5) conductive heating by means of heated blankets or sleeping bags.

Hot Humid Air Cabinets. — The device for inducing fever by physical means which is employed most commonly in this country is the hot humid air cabinet. A plan of one of the earlier models known as the Kettering hypertherm is illustrated in Fig. 12. One of the newer models of the hypertherm is illustrated in Fig. 13*a* and *b*. This type of apparatus was developed by Simpson and Kendell[1, 2] at the Kettering Institute for Medical Research in Dayton, Ohio. I have employed it extensively and have found it satisfactory for the production and maintenance of prolonged high fevers.

Warm humid air is circulated slowly through the cabinet. The air temperature varies between 110° and 130° F. (43.3° and 54.4° C.) and the humidity usually is kept above 80 per cent. Temperature and humidity

Cabinets Heated by Luminous Bulbs or Nonluminous Heat Coils — A fever cabinet heated by luminous bulbs can be constructed for about $150[3] Another one has been described[4] which can be built for considerably less than $100 The plan of such a cabinet which was developed by Sheard is illustrated in Fig 14 Sheard's cabinet differs from the other

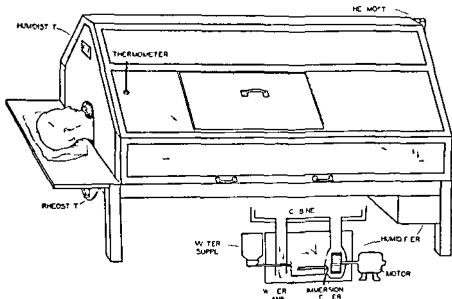


Fig 14 Plan of the Sheard luminous heat fever cabinet (From Krusen F H Physical Medicine Philadelphia Saunders 1941)

luminous heat cabinets in having a humidifying mechanism attached and in being more heavily insulated The other luminous cabinets mentioned depend on moisture from the perspiration of the patient to humidify the still air of the cabinet This latter plan is feasible because if the cabinet is kept closed the air soon becomes saturated with moisture as the patient's temperature rises and he begins to perspire

Various types of fever cabinets which have been heated by nonluminous heating elements have been marketed also This type of cabinet has not been employed so extensively as have other kinds of fever producing machines

Diathermy — A method of heating the entire body by means of conventional diathermy formerly was employed for the production of artificial fevers but this procedure now has become obsolete At present the newer short wave diathermy machines frequently are used for induction of

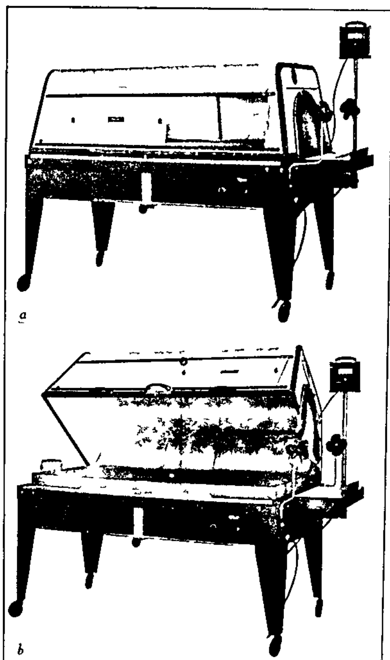


FIG 13 A metal fever cabinet known as the hypertherm which has been developed on the same principles as the original Kettering hypertherm (*a*) cabinet closed (*b*) cabinet open

are modified readily as desired so that the procedure is excellent because it permits such accurate control of bodily temperature

Hot Tub or Spray Baths — Tub baths can be employed to advantage for the induction of short low fevers Prolonged hot tub baths are depressing and may be dangerous Deaths from prolonged hot baths have been reported I frequently employ the short hot baths for therapeutic effects but these baths never are permitted to last more than an hour and usually do not last more than thirty minutes

The method consists of immersing the patient to the neck in water which is at a temperature of 105° to 110 F (40 5 to 43 5 C) He remains in the tub until his systemic temperature is within 1 5 F (0 83 C) of the desired level Then the water is cooled to the temperature of the patient or he is removed from the tub and placed in a blanket sleeping bag or insulated cabinet Usually his temperature will continue to rise until it reaches the desired level and will tend to remain there as long as he remains covered The method is comparatively safe and simple if it is not desired to increase the systemic temperature to more than 103° to 104 F (39 4° to 40° C)

Hot spray cabinets have been manufactured which resemble somewhat the other types of fever cabinets The patient s head protrudes from one end of the cabinet and his nude body is sprayed with a mist of nebulized hot water This form of fever apparatus has been used successfully in some institutions

Conductive Heating — Electrical blankets hot water bottles and blankets and fever bags all have been employed to heat and to insulate the body of the patient in order to produce artificial fever Unless some means of keeping the heavy coverings off the patient s body is employed all such methods are extremely uncomfortable Like hot baths they should not be used to raise the systemic temperature to more than 103° to 104° F (39 4° to 40° C)

Physical Principles Concerned in the General Application of Heat

The production of artificial fevers by physical means depends on two factors increased input and decreased output of heat energy Practically all of the methods for physical induction of fever employ both factors Some method of increasing temperature is used in conjunction with some method of insulating the body to limit loss of heat The input of heat generally is achieved by increasing the environmental temperature of the patient or by the application of high frequency currents and the egress of heat usually is lessened by placing the patient in an insulating medium of some sort

artificial fevers A common procedure is to introduce a long induction cable from a short wave diathermy machine into one of the humid air cabinets (Fig 15) The diathermy is used to induce the fever which then is maintained by means of the insulated cabinet I have obtained equally satisfactory results by induction of fever with the hot humid air alone and prefer this simpler method although there is no great objection to inducing the fever with diathermy

Halphen and Auclair[5] employed a powerful short wave diathermy ma

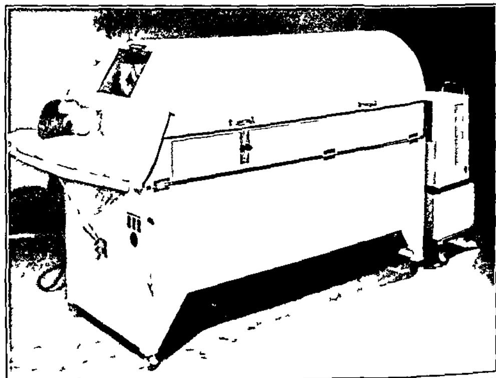


Fig 15 A fever cabinet into which extends a short wave diathermy induction coil Diathermy is employed to induce the fever which is maintained by the insulated cabinet (From Krusen F H Physical Medicine Philadelphia Saunders 1941)

chine and a nonmetallic treatment bed The patient dressed in a bath robe lay on the bed and was covered with blankets Two large flat diathermy electrodes were placed on the same plane beneath the bed at a distance of approximately 10 cm from the patient s back The patient s body thus was within the high frequency electrical field adjacent to the electrodes conversive heat within his body caused his systemic temperature to rise and loss of heat was prevented by the blankets The great objection to the use of blankets for insulation is that as the temperature rises the patient becomes uncomfortable under the heavy coverings

at 106 8° F (41 5 C) is one hour Nearly all strains of *meningococci* are attenuated greatly or destroyed at temperatures of 104° to 107 6° F (40 to 42 C) applied for five hours

Arthritis — Fever therapy has been employed in treatment for acute and chronic atrophic arthritis It seems of benefit in a certain percentage of the acute cases Short sessions of thirty minutes given every day or so seem to assist in controlling exacerbations of chronic atrophic arthritis

Bronchial Asthma — For bronchial asthma which has failed to respond to the usual therapeutic procedures fever therapy has been used Although this treatment has not been too successful nevertheless in some instances it has caused remission of symptoms for a year Usually the remission if it occurs at all lasts only for a few weeks

Sydenham's Chorea — Fever therapy now is considered by some authorities[8] the method of choice in chorea Of 76 collected cases of Sydenham's chorea in which fever treatment was given I found that in more than 72 per cent recovery occurred and in an additional 21 per cent marked improvement was noted Neymann's previous analysis of 69 cases indicated recovery in 77 per cent and improvement in 17 per cent

Endocarditis Lenta — The use of fever therapy in treatment for endocarditis lenta subacute bacterial endocarditis is particularly interesting In 1933 Bierman[8] employed fever therapy without additional chemotherapy for subacute bacterial endocarditis He reported that in this case showers of numerous emboli caused an exitus In 1936 I[9] reported that I had tried artificial fever therapy in endocarditis lenta and had abandoned it because of the apparently increased danger of embolism In 1937 Dry and Willius[10] treated four patients who had subacute bacterial endocarditis with fever therapy and came to the conclusion that despite the fact that fever therapy enhanced cellular reactions and bodily defense processes *Streptococcus viridans* seemed to be able to resist the highest temperatures which were humanly tolerable

In 1941 Bierman and Baehr[11] reported two cases of subacute bacterial endocarditis in which treatment with a combination of sulfanilamide and fever proved successful Their first patient was treated in 1938 In 1940 Bennett and I[1] following up Baehr and Bierman's successful 1938 case reported six cases of subacute bacterial endocarditis in which treatment with combined fever and sulfanilamide was unsuccessful The combined therapy in our opinion appeared to have a definite though transient influence on the disease for despite the ultimate failure culture of the blood following treatment revealed either a definite decrease in the number or a temporary complete disappearance of bacterial colonies

In 1941 Lichtman and Bierman[8] reported that of 200 cases of subacute

From a physical standpoint the regulation or prevention of loss of heat is more important than the application of heat in producing artificial fevers. This is owing to the fact that the heat eliminating mechanism of human beings when performing in a normal manner can rid the body of an excess of heat at a rate which is twelve times as great as the basal rate of heat production.

Action and Uses of Devices for the General Application of Heat (Fever Therapy)

High physically induced fevers increase the pulse and circulatory rates. The velocity of the blood may be increased as much as 400 per cent. During induction of fever the cardiac filling time is shortened temporarily so that partial decompensation may occur. When fever therapy is accompanied by profuse sweating the reduction in blood plasma may be so great that peripheral vascular collapse ensues. During fever therapy the visible capillaries of the nail beds are increased in size and number. Physically induced fevers produce leukocytosis. An initial decrease in the number of leukocytes is followed immediately by a tidelike increase; the new cells are added in waves for several hours after completion of the febrile session. The number of leukocytes then gradually diminishes and attains prefebrile levels in about twenty four hours. Leukocytosis is greater several hours after the end of the fever session than at its close. At the peak there may be more than 40 000 leukocytes per cubic millimeter of blood. There is a relative increase in neutrophils and a relative decrease in lymphocytes following fever therapy. Excessive perspiration accompanying fever therapy may cause a marked decrease in the chlorides of the blood serum.

At the beginning of a session of fever the content of oxygen and the oxygen combining power of the venous blood are increased. Despite this increase of oxygen the increased metabolic activity and the increased demand for oxygen in the tissues may result finally in anoxia of the tissues particularly if the circulation begins to fail because of circulatory collapse. The danger of anoxia and likewise the danger of circulatory collapse owing to loss of bodily fluids from excessive perspiration always are present during prolonged sessions of artificial fever.

The growth of certain organisms is destroyed or attenuated at temperatures induced by artificial fever. The *Neisseria gonorrhœæ* generally is destroyed at a temperature of 106° to 107 F (41 1° to 41 6° C) in 6 to 34 hours the mean number of hours being 16 1. The thermal death time of the *Treponema pallidum* at 102 2° F (39 0 C) is five hours and

at 106.8° F. (41.5° C.) is one hour. Nearly all strains of *meningococci* are attenuated greatly or destroyed at temperatures of 104° to 107.6° F. (40° to 42° C.) applied for five hours.

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bacterial endocarditis caused by nonhemolytic *Streptococcus viridans* in which the sulfonamide drugs were administered recovery occurred in 1? (6 per cent) Recovery occurred in 5 (11 6 per cent) of 43 cases in which combined chemotherapy and heparin were used and in 9 (20 per cent) of 45 cases in which combined chemotherapy and fever therapy (either physically induced or induced by typhoid paratyphoid vaccine) were employed They concluded The combined methods of therapy seem to promise a greater incidence of recovery than may be anticipated in the natural course of the disease or after treatment with sulfonamide drugs alone

The series of cases reported to date is too small to have any great statistical significance it is possible that the 6 failures reported by Bennett and myself happened to be drawn from the large group of patients who failed to respond In the light of present evidence therefore it seems logical to consider the use of combined fever and chemotherapy in this nearly hopeless group of cases Additional experience may modify this opinion At present there seems to be nothing better to offer Bierman and Baehr[11] concluded that their experience indicated that physically induced pyrexia enhances the value of chemotherapy in the treatment of subacute bacterial endocarditis Their clinical results supported the in vitro observations of White[13] that the effectiveness of the sulfonamide drugs is materially enhanced at sustained higher elevations of temperature

Gonorrhea — I have been interested especially in the treatment of gonorrhea by means of fever therapy and more recently in treatment by means of a combination of fever therapy and the sulfonamide drugs for gonorrhea which is resistant to chemotherapy alone In a series of 415 cases of proved gonorrhea in which adequate fever therapy was administered after an average of four fever sessions per patient Randall Stuhler and I found that there were apparent complete clinical remissions in 94 1 per cent[14] Follow up studies revealed that the disease recurred in not more than 3 to 5 per cent [15] Of 1 157 collected cases of acute and chronic gonorrhea treated by artificial fever I[16] found that apparent cures were reported in 87 4 per cent and failures in 12 6 per cent

Despite these excellent results with fever therapy alone with the advent of the sulfonamide drugs it became apparent that they would have a curative effect in a high percentage of cases of gonorrhea The administration of these drugs under proper control is certainly a much less rigorous procedure than is fever therapy Therefore it is recommended at present that chemotherapy be tried first before fever therapy is administered for gonorrhea

Chemotherapy has failed to cure gonorrhea in 3- per cent of the cases reported by Dees and Young[17] in their recent review of the literature. It is in this group of highly resistant cases, chemotherapy failures, that the combination of fever and chemotherapy seems to be particularly valuable. For such cases I now administer a single 10 hour fever at 106.8° F (41.5 C) at a time when there is a high hemal concentration of the sulfonamide drug. This is strictly an institutional procedure and should be attempted only by a well organized group of fever therapists.

I[16] found that in a group of 43 patients suffering from resistant gonorrhea, all of whom had failed to respond to unfortified sulfonamide therapy, an average of 1.2 treatments with combined chemotherapy and artificial fever for 10 hours effected apparent complete clinical remissions for 95.4 per cent. Thus it seems that the combined procedure is by far the most potent means of treating gonorrhea; this method always is to be considered when unfortified chemotherapy fails.

Kendell, Rose and Simpson[18] agree with me because recently they reported: All of 31 unselected consecutive patients treated with sulfanilamide or promin for eighteen hours before a single 10 hour fever session at a rectal temperature of 106.6° F were cured. They studied 83 patients suffering from complications of gonorrhea resistant or intolerant to chemotherapy. Of those refractory patients receiving fever therapy alone, only 12.5 per cent were cured following a single 6 hour treatment at 106.6° F; 62.5 per cent were cured following a single 10 hour treatment at 106.6 F.

I have been using the 10 hour sessions of fever at approximately 106.8 F (41.5 C) routinely for resistant gonorrhea since January 1937 because previously I had come to the conclusion that this was the most satisfactory way of treating resistant gonorrhea. The observations of Kendell and his associates confirm these views.

With the introduction of chemotherapy this procedure was combined with the 10 hour sessions of fever with even better results. Kendell and his associates observed that a 10 day period of intensive sulfanilamide therapy prior to fever therapy is without value in sulfanilamide resistant patients provided none of the drug is present in the body fluids at the time of the fever treatment. This confirms my previous contention that there must be a high hemal concentration of the drug at the time of the fever treatment.

Kendell and his associates came to a conclusion with which I agree, namely that: The combination of a single 10 hour session of artificial fever therapy combined with the administration of adequate sulfanilamide or promin for eighteen hours prior to the fever treatment appears

to be the procedure of choice in the treatment of chemotherapy resistant gonococcic infections

Gonorrheal Arthritis — Fever therapy is the most effective means of treatment for gonorrheal arthritis In the 'Fifth Rheumatism Review'[6] there was a summary of fifteen reports in which results of fever therapy in approximately 380 cases of gonorrheal arthritis were presented About 90 per cent of these 380 patients who had acute or chronic gonorrheal arthritis became free of symptoms Fever therapy was spoken of variously as specific the procedure of choice the best treatment now available and the treatment of choice to be used at the earliest available opportunity in cases of gonorrheal arthritis

Recent advances in chemotherapy undoubtedly have lessened the incidence of this later manifestation of gonorrhea But whenever chemotherapy fails to prevent the development of a gonorrheal arthritis the combined fever chemotherapy regimen should be attempted at once It is unwise to delay the combined procedure too long because the earlier the combined treatment is given the less is the likelihood of permanent damage to the involved joint or joints

Gonococcal Septicemia — There have been several reports[19, 20, 21, 22] of cases of gonococcal septicemia in which cure followed fever therapy In two instances[19] even though there was an associated gonococcal endocarditis recovery occurred In Elkins and my[43] case of gonococcal endocarditis in which fever therapy was used recovery did not occur In the light of present knowledge the combination of fever and chemotherapy always should be considered when gonococcal septicemia is encountered

Meningococcal Septicemia — For this condition combined fever and chemotherapy may be curative Elkins and I[43] reported successful employment of this procedure in one such case Four cases of meningococcal septicemia in which unfortified fever therapy has produced cures have been reported[4, 5] The combined procedure seems worthy of trial in selected cases of meningococcal infection

Multiple Sclerosis — Fever therapy although often recommended seems to be of limited if of any value for multiple sclerosis After *treating 10 patients with discouraging results I abandoned the procedure* A review of the conclusions of five other investigators[7, 6–9] led to the conclusion that the results of fever therapy for multiple sclerosis for the most part have been unfavorable[16] Recently Bennett and Lewis[30] checked 51 cases of multiple sclerosis for an average of thirty one months after artificial fever therapy Although they expressed the opinion that the procedure still should be tried early when the patients were ambu

latory without assistance they concluded that on the whole except in the early group of cases and those having signs which suggest infection there is little evidence that fever therapy has any markedly beneficial results in multiple sclerosis Furthermore they stated that in the bedridden group fever therapy does no good and may do harm

Mycosis Fungoides Neuritis and Radicular Pain —Fever therapy has been employed in treatment of mycosis fungoides with transitory improvement Of 10 cases reported in the literature[11, 12] moderate and temporary improvement was noted in 8 I have seen temporary but distinct improvement in 2 cases Fever therapy may retard the disease sufficiently to warrant its employment

For neuritis and radicular pain artificial fever of low temperature has been recommended[13] as a safe and efficient means of treatment

Rheumatic Fever —Treatment for rheumatic fever by means of physical fevers especially when combined with chemotherapy sometimes may be justifiable In one series of cases[14] there often was relief from pain and from swelling of joints as well as a final reduction in the number of leukocytes and in the sedimentation rate of the erythrocytes In two-thirds of this small series of 9 cases inactivity occurred in an average of 24 days after an average of 5 fever treatments

Syphilis —Investigations[15] of the treatment for early syphilis by physically induced fevers revealed that artificial fevers combined with antisyphilitic chemotherapy afford better results than can be obtained from the use of either one alone In an experimental study of the combined procedure for treatment of early syphilis it was found that artificial fever fortifies and intensifies the curative action of chemotherapeutic agents and that the time required for treatment can be reduced greatly by the combined treatment method In its present stage of development fever therapy cannot possibly be made available to the average patient who has a primary syphilitic lesion but it is possible that it may be employed routinely for primary syphilis at some future time A final evaluation of the procedure will not be possible for many years

For dementia paralytica physically induced fevers frequently can be used to great advantage There still is much controversy concerning the comparative value of physical fever and malarial fever in treatment for paresis Enthusiasts about malarial fever have been slow to recognize the undoubted effectiveness of physically induced fever for dementia paralytica

Probably the most authoritative comparative study of the relative merits of the two procedures is that recently published by physicians from a group of co operating clinics working in conjunction with the United States Public Health Service* This group whose chairman

was O'Leary carefully studied 1 100 patients who were treated with malaria as compared with 320 patients who received physically induced fevers The number of cases was large enough to be of some statistical significance and there was much evidence to indicate the slight superiority of physical fevers over malarial fevers

The Committee studied patients under treatment observation for three or more years Of the patients who had mild paresis 52 4 per cent of those treated with malarial fever and 59 3 per cent of those receiving physical fever obtained remissions Of those who had intermediate paresis 27 3 per cent of the patients who were treated with malaria and 28 1 per cent of those treated by physical fevers obtained remissions For severe paresis an even more striking difference was found only 0 8 per cent of the malaria treated group as compared with 12 0 per cent of those treated by physical fevers had remissions Furthermore the crude death rate in the malaria treated group was 13 4 as compared with only 8 1 in the cases treated with physically induced fever

In only one respect did the statistical evidence seem to reveal a superiority of the malarial therapy over the artificial fever therapy In patients treated with fever plus chemotherapy the annual rates of spinal fluid as well as blood reversal were consistently higher with malaria than with artificial fever But even here there was an explanation because this difference was assumed to be due to the greater amount of chemotherapy 17 per cent more administered to the malaria patients

More studies of course will be necessary but as evidence piles up it becomes increasingly evident that physical fevers are equally as effective if not more effective than malarial fevers in the treatment of dementia paralytica In addition any procedure which will lessen the mortality by more than 5 per cent should be given careful consideration

For tabes dorsalis fever therapy sometimes has been recommended In a report[1] of the results of this treatment of 15 patients 8 were said to be greatly improved 6 moderately improved and 1 was unimproved One of the most constant results has been relief of gastric crises and tabetic pains Another investigator[7] reported that two thirds of 114 tabetic patients exhibited definite improvement following fever therapy

Fever therapy has been reported also as being of much value in the treatment of ocular syphilis Culler[37] found the combination of fever and chemotherapy useful for syphilitic interstitial keratitis exudative uveitis and choroiditis

Telanus —An interesting case in which fever therapy was employed in my department as an adjunct in treatment for tetanus was reported recently by Heersema[38] In this case fever therapy was administered in

conjunction with the use of antitoxin. Despite the fact that he had failed previously to respond to large doses of antitoxin, when fever therapy was inaugurated the patient began to improve and he finally recovered. Heersema commented that "it is not impossible to postulate a more effective interrelationship of the toxin and antitoxin facilitated by the hyperthermia. For the present, however, the symptomatic relief obtained is sufficient to warrant further trial of this method. There was no doubt of this patient's improvement by the third day of treatment, whereas the clinical course before initiation of hyperthermia was definitely downward."

Malignant Tumors.—Warren[39] of Rochester, New York, has employed a combination of roentgen therapy and physical fever in treatment of malignant tumors. He stated that the growth of tumors is inhibited more completely by the combined procedure than by roentgen therapy alone. Jares[40] also working at Rochester, New York, studied the thermal death time of animal tumor cells in vitro. He came to the conclusion that the combined effects of fever and roentgen rays are superior to the effect of either alone. The most destructive combination was simple fractional doses of roentgen rays, about 300 r daily, plus fever treatment immediately afterward.

In a recent report[41] on the studies at Rochester, New York, on the combined effects of high voltage roentgen therapy and artificial fever on carcinoma the author stated: "The summative effects of the two radiations, x-rays and heat, appear to be more destructive to the carcinoma and normal structures than either alone. Since the dosage values are not well understood the experiments have been restricted to hopeless cases. The delayed effects (telangiectases, edema, cutaneous degeneration and the like) seem to be more marked, probably because of the summative effect.

"The following dosage has been used with safety, though it should not be attempted by any one not well versed in both irradiation technic and fever treatment technic. Daily for six days 250 roentgens is given in the usual manner for any one port. On the third day in this schedule a five hour fever bout at 41.5° C. (106.7° F.) rectal temperature is administered and at the end of the fever, while the body temperature is up, that day's x-ray treatment is given. A second fever bout of one hour (or more if the patient is not too much intoxicated by the tumor destruction) is given on the fifth day with the x-ray treatment again administered at its end. Several portals may be treated simultaneously except that great caution must be exercised not to overtreat (i.e., not over 1,800 roentgens given to any one skin area) within a given course. Courses have been repeated in six months without catastrophe, although the damage to the skin was considerable."

At present this method is purely experimental and is not advocated for general use until its merits are more clearly defined.

At this time there is no indication for the clinical employment of fever therapy as a therapeutic measure for malignant tumors.

Undulant Fever (Brucellosis).—Fever therapy has proved to be of distinct value in treatment for undulant fever. Prickman, Bennett and I[12] reviewed the results obtained in 21 cases of brucellosis following treatment by means of physically induced fever and found that in approximately 80 per cent apparently complete clinical remissions occurred. Recently Moor[13] reported on 15 cases of brucellosis treated by fever therapy. Nine patients, 60 per cent, obtained unqualified recovery; one was much improved, one was improved, and the other four were only temporarily improved. Zeiter[14] at the Cleveland Clinic and several others[15] also have reported successful treatment of brucellosis by means of fever therapy. Results have been most encouraging throughout, although the series still is small; there is increasing evidence of the value of fever therapy in this disease.

CONTRAINDICATIONS TO THE GENERAL APPLICATION OF HEAT (FEVER THERAPY)

Serious complications of fever therapy are heat stroke, heat exhaustion and circulatory collapse, which are followed by anoxia and finally hemorrhagic changes and damage to nerve tissues. Minor complications include tetany, heat cramps, delirium, mild dehydration with resultant nausea and vomiting, superficial burns and herpes labialis. Skillful treatment will prevent or minimize many of these complications. Important factors in management include the administration of sufficient amounts of fluid either orally or intravenously to prevent circulatory collapse, the employment of inhalations of oxygen throughout the treatment in order to prevent anoxia, and proper cooling of the patient in case the temperature becomes too high.

Apparently several deaths have occurred because of incorrect attempts at lowering bodily temperature during excessive hyperpyrexia. In several instances patients have been placed in ice packs in an attempt to lower rapidly their high systemic temperatures. Actually this procedure constricts the peripheral capillaries, lessens the amount of radiation of heat, drives the hot blood from the surface into the splanchnic regions and often causes a slight additional rise of the rectal temperature. The correct method of lowering the bodily temperature if it becomes too high consists of removing the patient from the fever producing device, sponging

his nude body with tepid water and turning a fan so that it blows across the surface of the body Bodily heat thus will be dissipated rapidly by evaporation and the high temperature will tend to fall rapidly to normal

A treatment as heroic as fever therapy is not without a definite element of danger According to the most accurate compilation I have been able to make the mortality rate per patient from fever therapy now is less than 0 2 per cent This compares favorably with the mortality from simple appendectomy In one average hospital 685 appendectomies were performed and there were 8 deaths a percentage mortality rate per patient of 1 16

Fever therapy is contraindicated in about the same conditions as is a major operation It should not be administered to patients who have severe cardiovascular renal disease evidences of damage to the liver or sensitivity to heat Its employment is contraindicated at the extremes of age The very young and the very old do not tolerate fever therapy well It always should be used with caution for patients who are asthenic or dehydrated A careful general physical examination and accurate laboratory studies should be performed before administration of fever therapy

SUMMARY OF DATA ON FEVER THERAPY

There are numerous effective methods for the general application of heat to the human body The procedure usually is called fever therapy Elevations of systemic temperature can be accomplished by means of heated cabinets diathermy hot baths or by heated blankets or packs The hot humid air cabinet seems to be the most satisfactory device for producing artificial fever by physical means

High artificial fevers produce profound physiological changes which have been investigated rather extensively in the past few years Fever therapy has become a therapeutic agent of considerable usefulness and it gives promise of being still more valuable as more information is ascertained concerning it

Fever therapy often is of value in treatment for resistant gonorrhea and its complications and for syphilis and its various forms The value of fever therapy for syphilis of the nervous system is becoming recognized It has been employed also to more or less advantage in the management of atrophic arthritis intractable bronchial asthma Sydenham s chorea endocarditis lenta meningococcal septicemia mycosis fungoides neuritis rheumatic fever tetanus and undulant fever The combined application of fever and chemotherapy apparently is going to be extremely useful in

a number of diseases Fever therapy requires a trained personnel and proper equipment In unskilled hands the procedure is potentially extremely dangerous The development of fever therapy is a distinctly valuable contribution to the advance of modern therapeutics

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LOCAL AND GENERAL APPLICATIONS OF COLD

Applications of cold both locally and generally have been employed for therapeutic purposes There has been considerably less investigation of hypothermy than of hyperthermy The therapeutic administration of cold has been called cryotherapy or crymotherapy and prolonged systemic applications of cold have been spoken of as hibernation or refrigeration therapy

Recently considerable unfortunate publicity has been given to the possibilities of benefiting carcinoma by such general applications of cold As yet there is no convincing evidence that any such possibility does exist While studies in a few cases have indicated that prolonged general applications of cold effect apparent modifications in malignant cells the number of cases studied is so meager as to preclude serious consideration at this time

Although local applications of cold long have been used in therapy the general application of cold has not been established as yet as a rational therapeutic procedure

Methods of Applying Cold

Cold water or ice can be applied directly or indirectly to a small or large area of the human body to produce local or systemic effects In some instances ordinary refrigerating units similar to those employed in the household electrical iceboxes are connected with metallic coils or blankets which are applied to the entire body of the patient in order to effect lowering of the systemic temperature

In other instances an air cooling unit similar to that employed for air conditioning of rooms in the summer is employed to cool a small room in which the nude patient lies on a bed in order that his systemic temperature may be lowered Another arrangement which I have seen consisted of a cold air blower connected to the top of a tent which was placed over the bed of the patient The cold air blew down over the patient and cooled him effectively In still another arrangement the patient is placed in a large bag containing within its walls serpentine coil through which is circulated a cooling fluid derived from a regular refrigeration unit which is placed at the foot of the patient s bed

For local application of cold the time honored ice bag the cold compress and the ice pack still are extremely useful A refinement of technic consists of the construction of sets of metallic applicators which can be connected to a refrigeration unit and through which the refrigerating mix

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Sept 1 1941

therapy because there have been so many recent inquiries concerning it and because its distinct limitations should be stated

Physical Principles Concerned in the Application of Cold

There is an extreme dearth of information concerning the physics of cold. Textbooks on physics neglect this subject in an amazing fashion. From a therapeutic standpoint, however, it is necessary merely to know that in order to apply cold to all or to a part of the human body it *must be placed in a cold environment or in contact with a cold substance*.

Action and Uses of Cooling Procedures

Cooling of the surface of the body without compensation produces definite systemic changes. Constriction of the peripheral vessels occurs with associated peripheral stasis and anoxemia. There is a lowered leukocytic response and the phagocytic capability of the fixed tissue cells is impaired. These changes are the reverse of those observed on applications of heat. Processes of immunity unquestionably are delayed in local regions which are cooled. Locally the volume of blood will be diminished and local metabolic activity will decrease. Application of cold to the abdomen tends to cause a temporary increase in peristalsis which is followed later by a decrease.

Placing the forearm in cold water lessens the rate of circulation so greatly that eventually even comparatively deep tissues may have a *temperature little higher than that of the bath. Local application of* cold to any region of the body will tend to cause generalized vasoconstriction. Drinking of cold water likewise causes vasoconstriction.

Hypersensitivity to cold occasionally is observed. Horton and his associates[1] studied 22 hypersensitive persons and noted that locally there was cutaneous pallor during exposure; redness, swelling and increased local temperature appeared on removal from the cold environment. After a latent period of three to six minutes the systemic reaction developed; this consisted of flushing of the face, a sharp drop in blood pressure, a rise in pulse rate, a tendency toward syncope and then transitory recovery in five or ten minutes. These studies suggested that a chemical substance which causes a histamine-like reaction is produced in the skin following exposure to cold.

Although in most instances applications of cold impair circulation, occasionally applications of mild cold which will cause slight vascular con-

ture is circulated (Fig 16) These small applicators can be applied to various regions or orifices of the body in order to administer intense cold Little is known as yet concerning the value of or indications for the use of these applicators which were constructed primarily for use in conjunction with hibernation therapy for malignant lesions The thought

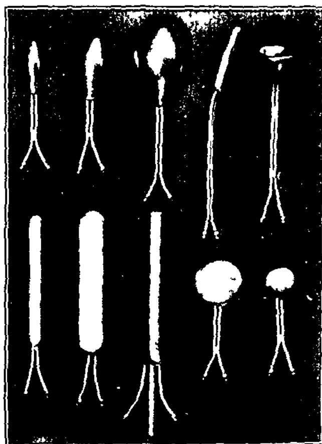


Fig 16 Applicators through which a cooling mixture can be circulated from a refrigeration unit to permit local application of intense cold

was that these applicators could be applied directly over the growth to produce additional local cooling during the period when the bodily temperature was lowered

I have had no personal experience with the method for treatment of malignant lesions by means of general and local applications of cold and sincerely doubt that the procedures ever will be of much if of any value Nevertheless it seems worth while to consider the whole subject of cold

for each degree Fahrenheit the temperature decreased The bleeding time has been shown[6] to be reduced in partially frozen animals

If the systemic temperature of rabbits is decreased to less than 75 2° F (24° C) frostbites will occur Shivering ceases at this temperature level and the lethal general temperature for rabbits is approximately 60 8 F (16 C) Oppenheimer has informed me that human beings cease to shiver as the body is cooled and shivering does not return as the body is gradually warmed again Large amounts of heat are required to restore the normal temperature of animals or human beings after cooling Troedsson[7] found that when the temperature of rabbits was lowered to 73 4° F (23 C) the number of leukocytes decreased from 10 300 to 5 200 per cubic millimeter the relative number of polymorphonuclear leukocytes increased and the lymphocytes decreased

Experimental studies by Meader and Marshall[8] revealed that mice were able to survive an internal temperature of 47 3 F (8 5 C) Cooling produces an initial acceleration of the respiratory rate which is followed by a reduction of rate The respiratory rate diminishes approximately 10 excursions per minute per degree centigrade of loss of heat until an internal temperature of 53 6 to 60 8 F (12 to 16 C) is reached Thereafter it diminishes approximately 20 excursions per minute per degree centigrade

Rapid freezing of aqueous suspensions of bacteria leads to death of a constant proportion of cells varying from about 80 per cent of the most sensitive organisms *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) to a slight percentage or no destruction of the least sensitive structures spores[9]

A significant study which suggests the futility of employing cold as a curative agent for malignant disease is that of Breedis and his associates[10] They found that although the transmitting agent of leukemia in mice presumably malignant leukocytes is inactivated by rapid freezing to −22° F (−30 C) it nevertheless remains viable even at −94 F (−70 C) when frozen slowly These investigators found also that sarcomatous tissue of mice can be frozen to at least −94 F (−70 C) without being inactivated and that this tissue can be preserved at this temperature with little or no subsequent deterioration during at least 56 days In the light of these facts it seems that it is utterly useless to attempt to destroy or to inhibit the growth of malignant cells in the living human being by gradual reduction of the systemic temperature to levels between +88 and 90 F (+31 1° and 32 2° C) for periods of five or six days

Local Applications of Cold — These have been employed therapeutically for conditions in which peripheral vasoconstriction is desirable Contusions sprains or other superficial traumatic lesions in which there

striction and moderate reduction of capillary pressure actually may cause a more rapid flow of blood than would application of heat

Reactions to thermal changes are very complex They are in general vasodilatation on heating and vasoconstriction on cooling If the cold is intense it may cause vasodilatation Arterioles capillaries arteriovenous aneurysms and veins are involved There may be considerable local increase or decrease in the flow of blood These changes are caused partly through nervous reflexes Application of cold to an extremity may cause vasoconstriction in a distant region such as an opposite limb which is not primarily affected by the change in temperature

Peripheral vasoconstriction caused by local application of cold is balanced by opposite changes in the remaining vessels particularly the splanchnic or other deep vessels Bazett has shown that the vasodilatation caused by extreme cold occurs only when the temperature of the skin is less than 64 4° F (18° C) The reflex that produces such dilatation probably is akin to a mild inflammatory reaction This reaction may protect the peripheral region from injury

Brooks and Duncan[3] recently have conducted interesting studies on the effects of temperature on the survival of anemic tissue These experiments demonstrated conclusively that temperature is a powerful factor in determining the length of time tissues rendered completely anemic remain viable Although usually it has been contended that in the presence of threatened gangrene the part should be kept in a warm *environment to maintain viability and to promote normal* circulation these investigators found that completely anemic tissues became gangrenous much sooner at high temperatures than at low ones Brooks in discussion stated that the experiments have convinced him of the inadvisability of applying unregulated heat to an anemic extremity and have at least raised the question of the possible benefits of the employment of a method for maintaining temperature of anemic tissue below that which it would assume under ordinary clinical conditions Here possibly is a new indication for the employment of local applications of cold

General applications of cold cause distinct changes in the circulation time These have been investigated carefully by Oppenheimer and McCravey[4] They observed the circulation time of human beings subjected to refrigeration and found that it was increased from an average of 17 2 seconds at normal bodily temperature to 23 5 seconds in the same individuals during hibernation They observed an apparent correlation between prolongation of circulation time and reduction in rectal temperature the circulation time increased approximately 5 per cent

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and his associates[10] previously mentioned the temperatures employed *could have little effect on the malignant cells*. *In normal tissues cold always will tend to produce devascularization shrinkage and tissue* damage which of course will be followed by repair with fibrous tissue

Therefore the hypotheses which have been set forth by Fay and his associates as bases for suggesting this form of therapy in cases of carcinoma are debatable The number of cases reported to date is so limited that the whole problem remains in the realm of pure conjecture I would not give the question so much attention here were it not for the fact that much publicity regarding this work has swamped me with numerous inquiries concerning it

Until definite proof is forthcoming it seems evident that no clinician is justified in employing the procedure as a therapeutic measure in carcinoma unless he desires to do so from an experimental angle in an institution properly equipped for such investigative work

Systemic applications of cold have been suggested in treatment for lymphatic leukemia but again the studies of Breedis and his associates[14] suggest the futility of the method and there is no clinical proof of its effectiveness Troedsson[7] stated that mild generalized hypothermy might be found useful in reducing a temporarily high fever a high metabolic rate or rapid cardiac action to give the heart a rest At present none of these procedures has been investigated sufficiently to warrant its general use Currently local applications of cold can be said to be of clinical value but systemic applications of cold have not been developed to a point at which they can be employed in clinical practice

Contraindications to Applications of Cold

Cold should not be employed for patients who have a definite hypersensitivity to it nor should it be applied to the skin in the presence of cutaneous atrophy radiodermatitis or melanotic nevus It has been suggested[15] that prolonged cold therapy for inflammations may lessen vitality and hinder repair

The danger signs noted during systemic application of cold include slowing of pulse and respiration and lowering of blood pressure Although general applications of cold have not been employed sufficiently for one to define the contraindications clearly it seems obvious that the procedure should not be employed in asthenic individuals or in the presence of any marked circulatory or renal disturbance Respiratory infections also would seem to contraindicate its employment Acute pancreatitis has occurred following refrigeration therapy

is danger of extravasation of blood and lymph into the perivascular tissues often can be treated best during the first forty eight hours by local applications of cold

Cold often is applied locally for acute inflammation or congestion of superficial regions in order to produce vasoconstriction and to relieve pain but cold cannot be used to allay inflammations within the abdomen because now it is believed generally that local application of cold to the abdomen produces little if any change in the temperature of the underlying viscera Intense cold can be used to destroy superficial cutaneous lesions Usually a carbon dioxide pencil is employed for this purpose

Occasionally when a local rise of temperature in an extremity is desirable and a rise of systemic temperature is contraindicated the general rise can be avoided by placing another extremity in moderately cold water while the affected extremity is being heated This is known as the Loven reflex

Patients who are hypersensitive to cold can be desensitized by the simple expedient of immersing one hand in cold water at a temperature of 50° F (10° C) for one or two minutes twice a day for three or four weeks[1]

Systemic Applications of Cold —These have been tried clinically for patients who have advanced malignant disease In some instances local applications of cold have been used in conjunction with the general cooling Theorizing that increased temperature alone is required to bring into existence activation of the rapid embryological cellular division in hen s eggs that in plant life darkness and sustained abnormally high temperatures give rise to overgrowth and delayed maturity and that intense sunlight and sustained low temperatures tend toward a slow and stunted maturity Fay and Henny[11] advocated trials of refrigeration in cases of carcinoma They reported five cases in which responses were noted They claimed definite relief of local pain and apparent gross retardation in growth as well as diminution in the size of the carcinomatous lesions

Later *Smith and Fay*[1] *expanding on the hypothesis* that carcinomatous metastatic lesions are most common in bodily segments in which the temperature is highest again advocated refrigeration therapy They reported that local application of cold at approximately 36° F (2 2° C) to the pelvis of a patient who had a massive pelvic extension of a carcinoma of the cervix caused relief from pain in 48 hours that within 5 days there was devascularization of the carcinomatous region with shrinkage and within 3 weeks there was evidence of repair with fibrous tissue

Prolonged intense cold applied to normal tissues could be expected to produce much the same effects and in the light of the studies of Breedis

ULTRAVIOLET RADIANT ENERGY

Ultraviolet therapy consists of treatment by means of radiation from the ultraviolet portion of the electromagnetic spectrum (Fig 11) Sun light particularly during the summer months is a more or less satisfactory source of ultraviolet radiation The wavelengths of ultraviolet rays vary between 13 6 and 390 millimicrons

Ultraviolet rays with wavelengths between 13 6 and 290 millimicron are spoken of as far ultraviolet rays those with wavelengths between 290 and 390 millimicrons as near ultraviolet rays Properly employed ultraviolet radiation has a considerable field of usefulness in medicine

Methods of Applying Ultraviolet Radiant Energy

There are several sources of ultraviolet energy which can be employed for therapeutic purposes These include the sun various types of quartz mercury vapor arcs and carbon arcs To select a source of ultraviolet radiation it is necessary to know which rays the source produces their quantity and their physiological effects Different ultraviolet lamps produce different amounts of radiation from various regions of the spectrum Because of these variations different types of ultraviolet lamps may produce distinctly different physiological effects

It is apparent that the user of such a lamp must know the rays produced and their effects Practically all sources of ultraviolet radiation commonly employed produce not only ultraviolet rays but also visible and infra red rays

The Sun — Radiation from the sun has its spectral limits at about 290 millimicrons in the ultraviolet portion of the electromagnetic spectrum and 4 000 millimicrons in the infra red portion The greatest intensity is at about 490 *millimicrons The sun emits very* little ultraviolet radiation of wavelengths shorter than 350 millimicrons The intensity of the rays of wavelengths of less than 350 millimicrons is slight the intensity then increases rapidly to 490 millimicrons and above that decreases gradually to 4 000 millimicrons in the infra red region Sunlight contains approximately 1 to 5 per cent ultraviolet radiation 41 to 45 per cent visible or luminous radiation and 52 to 60 per cent infra red radiation

The sun is an unreliable source of ultraviolet radiation because it emits an appreciable amount of such rays especially during winter only for about three or four hours in the middle of the day The intensity of ultraviolet radiation is much greater at high altitudes than at sea level

SUMMARY OF DATA ON COLD APPLICATIONS

Local or general applications of cold will cause profound physiological changes There are numerous methods of applying cold therapeutically There are several indications for the local applications of cold Chief *among them are traumatic lesions inflammations and congestions* General application of cold is still in the experimental stage of development and there are at present no indications for its clinical employment

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Much of the radiation is absorbed by water vapor at the lower atmospheric levels

The Quartz Mercury Vapor Arc — Radiation from the quartz mercury arc lamp consists of a series of intense spectral lines namely at 257 265 280 297 302 313 334 and 365 millimicrons superimposed on a faint continuous spectrum extending throughout the visible and into the infra red region The radiation from such a lamp is composed of approximately 6 per cent far ultraviolet rays which have a high germicidal action and which are completely absent in sunlight 28 per cent total ultraviolet rays 20 per cent luminous rays and 52 per cent infra red rays

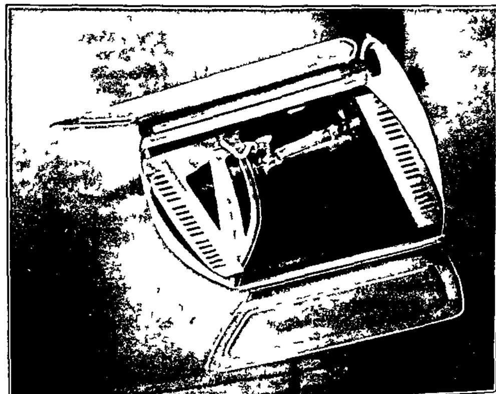


Fig 17 A quartz mercury vapor arc lamp

Quartz tubes containing a mercury vapor arc usually are enclosed in an adjustable reflector and applied over large regions of the body for purposes of general irradiation (Fig 17) Smaller quartz tubes containing a mercury arc sometimes are enclosed in a water jacket to cool the burner so that it can be brought close to the skin These water cooled quartz lamps often are called Kromayer lamps

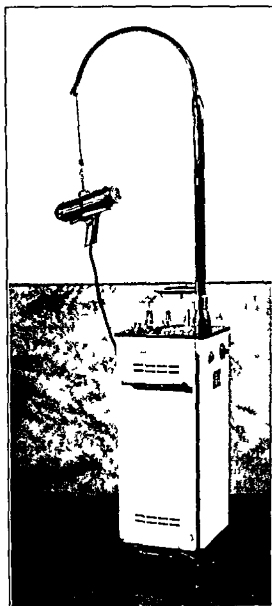


FIG 18 A new type of air cooled Kromayer lamp

Recently an air cooled Kromayer lamp (Fig 18) has been developed for local irradiation this is rather similar to the old water cooled units

with the exception that the small burner is cooled by means of an air blower and not by circulating cold water. Quartz rods and disks can be placed over the window of this lamp for the purpose of conducting the radiation to the surface or to the orifice which is to be exposed (Fig. 19).

The Carbon Arc. — Radiation from a carbon arc lamp varies according to the kind of carbon pencils employed. Electrodes of pure carbon are not employed therapeutically. The pencil like carbon electrodes contain a core composed usually of metallic salts. By varying the constituents of these cores the arc can be altered and its radiation modified.

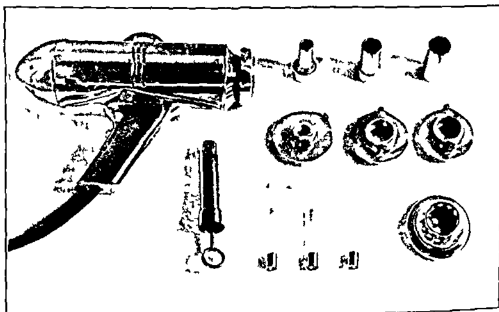


FIG. 19. Quartz disks and rods which are employed with the Kromayer lamp to conduct the radiation into bodily orifices or to small local regions of the body.

Carbons which contain such metallic cores are spoken of as "impregnated carbons."

The "A" or "sunshine" carbon. The type of carbon most commonly used in therapeutic lamps is known as an "A" or "sunshine" carbon. It is impregnated with "rare earth" oxides and its arc produces radiation which has a spectral range from 220 millimicrons in the ultraviolet region to more than 4,000 millimicrons in the infra red region. The spectrum which it produces approaches that of sunlight but still is far from being an exact match. Radiation from this source contains 5 per cent ultraviolet rays, 50 per cent luminous rays and 45 per cent infra red rays.

The B carbon The B carbon is similar but it is impregnated with iron oxide and its spectrum more nearly resembles that of the mercury arc This carbon is particularly rich in radiation of wavelengths shorter than 310 millimicrons

The C carbon The C carbon is impregnated with calcium oxide and is particularly rich in radiation in the region between 290 and 3[illegible]0 millimicrons Its arc emits 9 per cent ultraviolet rays 24 per cent luminous rays and 67 per cent infra red rays

The E carbon The other type of carbon which commonly is employed therapeutically is known as the E carbon The radiation which is emitted by its arc is similar to that produced by a tungsten filament lamp it is therefore a good source of near infra red rays *The radiation is particularly rich in rays from the spectral region between* 550 and 750 millimicrons in the orange and red portions of the visible spectrum It emits much radiation in the near infra red region

Usually therapeutic carbon arc lamps consist of two carbons arranged end to end in a suitable reflector (Fig [illegible]0) The carbons are connected to a source of electricity When they are brought together momentarily the electrical circuit is completed and then when they are separated slightly an intense electrical arc forms between the tips of the carbon electrodes The carbon electrodes are consumed gradually and must be replaced from time to time

The chief advantage of the carbon arc lamp is that the carbons can be changed to vary the radiation produced Thus different therapeutic effects can be achieved with the same lamp

The Cold Quartz Lamp — In the past few years an ultraviolet lamp which is practically devoid of heat has been marketed It therefore has been called a cold quartz lamp It consists of quartz tubing containing neon and mercury vapor through which is passed an electric charge of high voltage The appearance of the tubing is similar to that of the familiar neon signs commonly used in advertising This tubing usually is shaped into a serpentine grid which is placed over the face of a reflector

The radiation from this lamp consists of one very intense spectral line at 254 millimicrons and a series of a few much less intense lines The lines at 297 and 313 millimicrons are fairly intense but 95 per cent of the total radiation of wavelengths less than and including 313 millimicrons is contained in the resonance emission line at 254 millimicrons Because of its limited range of radiation this type of lamp has a limited field of usefulness

Sun Lamps — In the past few years several kinds of sun lamps have been constructed for home use Typical of this group of lamps is the

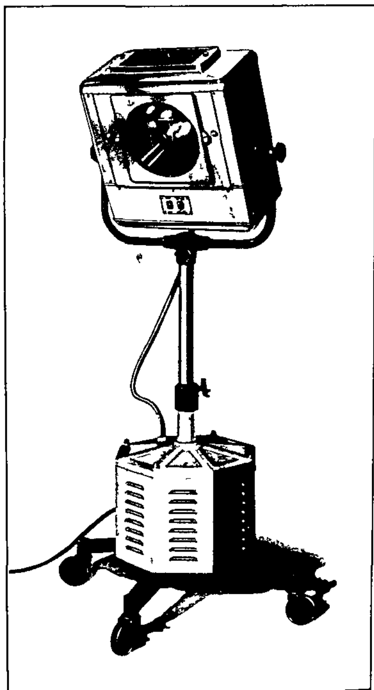


FIG 20 A carbon arc lamp of the type commonly employed in a physician's office

S-1 lamp It consists of a tungsten filament two tungsten electrodes and a drop of mercury enclosed in a bulb of ultraviolet transmitting glass When it is turned on the filament becomes hot and the mercury vaporizes and forms a mercury vapor arc between the electrodes This arc emits ultraviolet rays (Fig 21) The radiation is not unlike that of the other

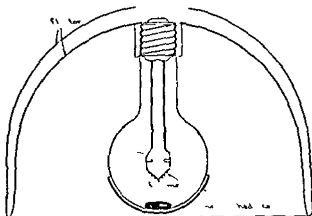


Fig 21 An S-1 lamp which is a suitable source of ultraviolet radiation for use in the home (From Krusen F H Physical Medicine Saunders Philadelphia 1941)

hot mercury quartz lamps It emits 5 per cent ultraviolet rays 78 per cent luminous rays and 17 per cent infra red rays At a distance of - feet 60 cm its output of ultraviolet rays is about equivalent to that of noontime sunlight in June

Other similar sun lamps which recently have been approved as suitable devices by the Council on Physical Therapy of the American Medical Association are the S-4 lamp and the L M-4 lamp Still another suitable sun lamp which produces radiation similar to that of the S-1 lamp is the type G mercury glow lamp These lamps will not be described in detail

Physical Principles Concerned in the Application of Ultraviolet Radiant Energy

The electromagnetic spectrum already has been mentioned briefly The physician who uses ultraviolet radiation therapeutically must be familiar with the properties and the effects of the rays derived from various portions of this spectrum if he is to use his lamp intelligently

The unit of measurement of wavelength of radiation which is employed commonly by the United States Bureau of Standards is the milli

micron, usually abbreviated mμ. The other unit of measurement of wavelength which sometimes is employed, is the Angstrom unit, usually abbreviated A. U. or A.° An Angstrom unit is 0.1 millimicron (Table I). The electromagnetic spectrum is represented in graphic form in Fig. 11 and in tabular form in Table II.

The ultraviolet rays with wavelengths ranging between 13.6 and 390 millimicrons possess varying physical properties and produce a variety of effects which are chiefly of a chemical nature. For example, there is a band of ultraviolet rays between 290 and 315 millimicrons, sometimes called the "vital ultraviolet band," which possesses antirachitic properties and which converts more than 60 per cent of the provitamin ergosterol or 7-dehydrocholesterol into vitamin D. On the other hand, the group of ultraviolet rays, the wavelength of which is shorter than 280 millimicrons, are chiefly bactericidal and abiotic, capable of destroying tissue cells, and tend to destroy vitamin D.

It is apparent that, to obtain the maximal antirachitic effect from a source of ultraviolet radiation, the lamp used should produce little or none of the rays of wavelength shorter than 290 millimicrons and should be rich in radiation from the "vital ultraviolet band." Similarly, if a maximal bactericidal effect is desired, a source rich in the ultraviolet rays of shorter wavelength should be employed.

Penetration of ultraviolet rays through the skin or through mucous membranes never exceeds a depth of 2 mm. Various substances not only absorb such radiation but also reflect some of the rays. The most absorbent substance will reflect some of the rays, and conversely the most efficient reflector will absorb some of the radiation. The amount of absorption by human tissues depends largely on the wavelength of the radiation and the output of energy from the source.

ACTION AND USES OF ULTRAVIOLET RADIANT ENERGY

Exposure to ultraviolet rays produces[1] photochemical effects with activation of certain substances in the skin and also possibly in the blood. Also certain biological effects have been observed, such as stimulation of metabolism and growth and increase of circulation and cellular activity.

Ultraviolet rays of wavelengths between 290 and 315 millimicrons have the specific property of preventing and curing rickets. Radiation from this same "vital" region possesses the ability to impart an antirachitic potency to fats, milk, ergosterol, 7-dehydrocholesterol (the sterol found in human skin which can be activated), oils and vegetables. If pregnant or

TABLE I

UNIT OF MEASUREMENT OF WAVELENGTHS

One angstrom unit (A U or A)	One tenth millimicron or one ten millionth millimeter
One millimicron (mμ)	Ten angstrom units or one millionth millimeter
One micron (μ)	One thousandth millimeter
One millimeter (mm)	One tenth centimeter or one thousandth meter

TABLE II

ELECTROMAGNETIC SPECTRUM

Rays		*Extent of wavelength*
Gamma rays		0 0011 to 0 14 mμ
Roentgen rays		0 14 to 13 6 mμ
Ultraviolet rays	far	13 6 to 90 mμ
	near	90 to 390 mμ
Visible rays	violet	390 to 450 mμ
	blue	450 to 490 mμ
	green	490 to 550 mμ
	yellow	550 to 590 mμ
	orange	590 to 630 mμ
	red	630 to 770 mμ
Infra red rays	near	[illegible] to 1 400 mμ
	far	1 400 to 15 000 mμ
Hertzian waves		15 000 mμ to several kilometers

nursing mothers or cows are exposed to these rays their milk will develop an antirachitic potency

Ultraviolet rays will cause a delayed or latent erythema in the skin

of human beings Repeated exposures to erythemal doses lead to the production of diffuse pigmentation of the skin of the white man Such pigmentation probably assists in the absorption of radiant energy which is transformed into heat

There is evidence to indicate that ultraviolet irradiation of the human *being causes improvement of the tone color and elasticity of the skin and* presumably also increases the secretory and protective powers of the skin Exposures of large portions of the cutaneous surface to ultraviolet radiation produces activation of a constituent of the cutaneous cholesterol 7 dehydrocholesterol to form vitamin D which in turn stimulates absorption of calcium and phosphorus from the intestinal tract and increases metabolic efficiency Phytosterol of plants is activated similarly

It has been reported that ultraviolet irradiation causes an increase of the active oxygen content of the lipids of the skin and consequently an increase in their bactericidal action It is possible also that exposure to ultraviolet rays leads to the formation of hormones in the skin and accomplishes the activation of useful cutaneous reflexes

On general exposure to ultraviolet radiation the number of erythrocytes leukocytes blood platelets and hemoglobin of the circulating blood may increase slightly and the hydrogen ion concentration coagulation time and eventually the volume of blood may decrease In general darkness produces a reverse effect with the exception that the blood volume seems to be diminished Exposure to ultraviolet rays produces an increase in serum globulin Ultraviolet irradiation is believed to cause a possible increase in bodily resistance by increasing the bactericidal power of the blood which depends largely on the leukocytic reaction Such radiation probably does not influence specific immunity

In moderate doses ultraviolet radiation causes an increase in carbon dioxide tension and a relative alkalosis while in heavy doses it produces a decreased carbon dioxide tension and acidosis It has been *demonstrated* that ultraviolet irradiation causes a lessening of the toxicity of the serum of the patient who has pernicious anemia

General ultraviolet irradiation produces a transient lowering of blood pressure The factors which probably are responsible for the reduction of blood pressure are the production of cutaneous hyperemia the decrease in the viscosity of the blood the development of cutaneous depressor substances and the production of sympathetic hypotonia Activation of the circulation has been attributed to the vasodilating effect of the ultraviolet erythema and its continuous tonic action on the nerve endings It has been shown also that these rays cause increased permeability of cell membranes and capillaries

In general ultraviolet rays of wavelengths longer than 290 millimicrons produce presumably stimulative effects on the human body but if the rays are of wavelengths shorter than 290 millimicrons and in large quantities they will have a lethal effect on the cells of the human body In smaller quantities the rays of shorter wavelength may have a stimulative action on the cell These effects are due perhaps to the production of a toxic photo product which in large quantities is lethal and in small quantities acts as a stimulant to cell division

Other general effects of ultraviolet irradiation have been noted these include improvement of muscular tone increase in protein and mineral metabolism possible lowering of sympathetic tone possible stimulation of intracellular oxidation and possible increase in the rate of bodily growth

The application of ultraviolet rays does not act as a substitute for dietary deficiencies but produces an increase in the ability of the organism to utilize more effectively materials which are present but are not otherwise available It is said that general exposure to ultraviolet rays causes a decrease in the rate but an increase in the depth of respiration

Finally ultraviolet radiation has a definite bactericidal action The line at 266 millimicrons is the most highly bactericidal it is followed in order of effectiveness by the lines at 254 280 248 and 270 millimicrons It has been demonstrated recently that the very short rays with wave lengths of less than 240 millimicrons have some germicidal action Stimulation of bacterial growth has not been observed to result from exposure to ultraviolet rays

The use of ultraviolet radiation in the treatment of disease has been most extensive but much of the literature on the subject has been written poorly and is of an unconvincing nature It is essential therefore that physicians make a careful analysis of the writings on this subject and accept only those which seem to have proved their claims by properly controlled studies

Diseases of the Alimentary Tract — There is now sufficient evidence to indicate that ultraviolet irradiation may be of distinct value in the treatment of *tuberculous peritonitis and enteritis* Since intestinal tuberculosis is one of the most frequent complications of pulmonary tuberculosis occurring as it does in from 50 to 80 per cent of all fatal cases any measure that will be of benefit is of the utmost importance Ultraviolet irradiation is *one of the most important* factors in the arrest and treatment of intestinal tuberculosis In a survey of the records of 8 087 routine postmortem examinations evidence of pulmonary tuberculosis was found in 886 cases and of intestinal tuberculosis in 233 cases The ratio of pulmonary to intestinal tuberculosis was therefore approximately

4 1 Of 180 patients who had intestinal tuberculosis and had received treatment at Saranac Lake 65 per cent of those treated with ultraviolet light were alive whereas of those not so treated only 17 per cent were alive at the time of the report At the Trudeau Sanatorium of a series of 106 patients who had intestinal tuberculosis 88 per cent of those treated by ultraviolet light survived whereas only 25 per cent of those not so treated survived

Following the use of the mercury quartz lamp in the treatment of intestinal tuberculosis tubercle bacilli often disappear from the stools pain nausea and vomiting are relieved but the diarrhea and intestinal disturbances tend to resist the longest In the treatment of tuberculous peritonitis the best results are obtained in the ascitic type In abdominal tuberculous adenitis it may be unwise to temporize with light therapy since in more than three fourths of the cases it is possible to excise the affected glands

Ultraviolet irradiation has been recommended in the treatment of *pylorospasm* It is possible that when this condition as seems often the case is associated with calcium deficiency ultraviolet irradiation may be of value

Diseases of the Blood and Circulatory System — In the treatment of *secondary anemia* it has been suggested that one of the important factors in an ideal program consists of adequate exposure to ultraviolet radiation There is considerable similarity between anemia and rickets a disease cured and prevented by ultraviolet irradiation when there is an adequate intake of calcium and phosphorus In both diseases there is lowered gastrointestinal acidity pH which interferes with the absorption of calcium and with the absorption of iron with a resultant decrease in the amount of iron available for regeneration of blood In both diseases changes in the bone marrow and modifications in the types of cells may be seen Ultraviolet irradiation may be beneficial in the treatment of either disease

In a study conducted for a period of more than eight years in an artificial light clinic for school children it was found that after twelve or more exposures to irradiation from a carbon arc lamp the amount of hemoglobin of anemic children increased by approximately 10 per cent Another controlled study of the use of ultraviolet irradiation in 54 cases of secondary anemia indicated greater increases in hemoglobin and in the number of erythrocytes and leukocytes in the treated than in the control group It has been suggested that further studies of patients who have secondary anemia may indicate a possible influence of ultraviolet irradiation on the chemical constituents of the blood Although various studies

indicate that ultraviolet radiation may be a useful adjunct in the treatment of secondary anemia there are still insufficient data to indicate the exact value of this therapeutic measure

Various observers have shown that ultraviolet irradiation does produce transient *reduction in blood pressure* The work of Laurens[3] and his coworkers in this field has been most convincing As a therapeutic measure however it is doubtful whether ultraviolet irradiation can be considered more than a slight adjunct to the treatment of hypertension

Ultraviolet irradiation has been employed for *carbon monoxide poisoning* because Haldane and Hartridge showed that the dissociation of carbon monoxide and hemoglobin was increased markedly under the influence of ultraviolet light Such treatment has been found to be beneficial

Diseases of the Respiratory System — Many articles have been prepared pro and con with regard to the use of general ultraviolet irradiation in the prevention and treatment of the *common cold* At Cornell University[4] small groups of male students were irradiated with minimal erythema doses of ultraviolet rays once weekly during the winter months There was an apparent reduction in the incidence of colds ranging from 27 9 to 55 5 per cent At Vanderbilt University[5] an investigation on the management of common colds revealed decided improvement in cases in which ultraviolet irradiation was used

At the Cook County Hospital[6] ultraviolet irradiation was recommended in the treatment of *chronic coughs* It was said to have a stimulating effect on general metabolism and on resistance to infection provided the optimal dose was not exceeded and the patient was free from fever

On the other hand some investigators have been of a contrary opinion thus it has been concluded that although the mercury quartz lamp has been used extensively to enhance individual resistance to colds well controlled studies on both infants and adults nevertheless have failed to corroborate claims for its value Hill and Clark[7] found little to support the view that ultraviolet irradiation was capable of increasing a person s natural resistance Other investigators have performed experiments similar to those conducted at Cornell with results which were for the most part negative although they did find that in certain tests the resistance of the irradiated group was greater than that of the control group Still other investigators observed 363 adults for thirty five weeks during the first thirty one weeks approximately half the group were given frequent ultraviolet irradiations a single minimal erythema dose being applied either to the chest or to the back at each treatment The incidence of colds during the period of study was slightly higher in the irradiated group than in the control group However it should be pointed out that failure

to benefit from treatment may have been due to inadequate dosage Only a quarter of the body was treated at any session and the dose was not increased at subsequent sessions It is agreed generally that to produce beneficial systemic effects a series of irradiations to the entire body should be given and that the dose should be increased gradually

Further investigations will be necessary before final conclusions can be drawn concerning the value of ultraviolet irradiation in treating common colds

In the treatment of *pulmonary tuberculosis* there likewise has been much controversy concerning the use of ultraviolet irradiation Although ultraviolet light frequently is used in Europe for the treatment of pulmonary tuberculosis in this country it often has been thought to be dangerous It has been stressed especially that there is danger of producing pulmonary hemorrhage My own controlled studies[3] on 60 patients who were receiving routine sanatorium care indicated that hemoptysis did not contraindicate the judicious employment of heliotherapy and a number of other investigators have reached similar conclusions following controlled studies It has been said that treatment which brings about improvement in the general health of the patient is the best means of combating pulmonary as well as surgical tuberculosis

Observations on 115 patients treated by carbon arc irradiation led to the conclusion that minimal moderately advanced or even far advanced pulmonary tuberculosis may be benefited by graduated irradiation if the patient s temperature does not rise above 37 5° C (99 5° F) and his general physical condition is satisfactory In Denmark treatment of pulmonary tuberculosis with light now is almost universal and in Britain detailed results in a series of 123 cases led to the conclusion that if patients are selected carefully chronic pulmonary tuberculosis may be treated not only with safety but with good results

Recently a number of writers in the United States have expressed a similar opinion It has been reported that clinical experience will convince one of the value of the mercury quartz vapor lamp in the treatment of pulmonary tuberculosis of children Tuberculous infants who have excessive pulmonary infiltration even with cavity formation may recover

Although I believe that, judiciously employed in conjunction with routine institutional care light therapy may be of value as an adjunct in the treatment of pulmonary tuberculosis its indiscriminate use is fraught with danger Of 71 competent observers 47 obtained favorable and 24 either poor or no results following the use of ultraviolet irradiation in the treatment of pulmonary tuberculosis This indicates an

almost 2 1 preponderance in favor of the judicious application of ultra violet radiation For far advanced toxic or advancing active exudative pulmonary tuberculosis light therapy should not be employed but incipient pulmonary tuberculosis especially of children and nontoxic lesions which have reached the stage of chronicity may be benefited by the careful administration of small doses of general ultraviolet radiation Abundant rest an increased intake of food and proper hygienic measures are more important in the treatment of tuberculosis than is ultraviolet therapy which is merely an adjunct to these other measures

Diseases of the Bones and Joints — In a study of 22 children who had *tuberculosis of the bones or joints* and were treated throughout the winter and spring with radiations from a carbon arc light of high intensity it was found that the majority showed a rise in the blood count a tendency to gain weight and likewise a marked improvement in the local tuberculous lesions

An extensive study on the nonoperative treatment of *tuberculous joints* of the lower extremities revealed that over a period of years 65 per cent of the adult patients under treatment for all extrapulmonary tuberculous lesions had definite though usually inactive pulmonary tuberculosis Conservative treatment by heliotherapy in conjunction with routine care was used in this large series of cases Of 437 patients with tuberculosis of the bones and joints and 72 with nontuberculous osteomyelitis who remained on an institutional regimen for three months or longer the following conditions were revealed on dismissal 53 8 per cent apparently had recovered the tuberculosis of 23 1 per cent was arrested 10 7 per cent were improved 7 8 per cent were unimproved and 4 5 per cent had died A follow up of these patients revealed that between 80 and 87 per cent were working an additional 8 to 10 per cent were ambulant but unable to work and between 3 and 5 per cent were confined to bed It was concluded that such conservative treatment usually resulted in healing with useful motion Operative interference should not be attempted until after prolonged heliotherapy has been tried

Bernhard[9] as a result of twenty five years experience was of the opinion that in the treatment of *surgical tuberculosis* heliotherapy was the method of choice In his first 1 000 cases of surgical tuberculosis in which heliotherapy was employed 858 patients were cured 120 were improved 14 were unimproved and 8 had died a mortality rate of only 0 8 per cent Six of the patients who were unimproved died later raising the final mortality to 14 or 1 4 per cent The effect of heliotherapy in one case is shown in Fig 22

Osteomalacia fragilitas osseum and *delayed union of fractures* are con

ditions which may be due to faulty calcium metabolism and ultraviolet irradiation may be of value In a study of experimental fractures of the fibula in 25 normal dogs and 80 normal rats measured amounts of carbon arc radiation were administered during the period of healing During



FIG 22 Patient with extrapulmonary tuberculosis (a) before heliotherapy in April 1927 (b) after heliotherapy in December 1927 (Courtesy of Dr Richard T Ellison from Krusen F H Light Therapy Ed 2 Hoeber New York 1937)

this period 73 9 per cent of the fibulas of animals irradiated with sunshine carbons 26 9 per cent of those irradiated with C carbons and 41 3 per cent of those of the controls healed The average healing time for fractures was 3 7 days shorter when the animals were irradiated than when they were not In fractures of the long bones it has been reported that among patients who were given irradiated ergosterol the density

and the amount of callus increased as compared with a control group of patients These changes were greatest in children and in the aged and they began to appear about three weeks following injury On the other hand in rabbits and rats given respectively 3 and 1 25 gm of irradiated ergosterol by mouth the rate of healing or amount of callus in fractures of the tibia and fibula did not increase

In rats on which parathyroidectomy has been performed with consequent parathyroid deficiency calcification does not occur regularly in the callus following fracture if calcium is lacking also in the diet under such conditions administration of irradiated ergosterol promotes calcification of callus

It seems logical to presume that ultraviolet irradiation has little influence on healthy individuals whose calcium metabolism is normal but it would seem that it might be of value for patients with faulty calcium metabolism who sustained fractures

A number of authors have recommended the use of ultraviolet radiation for both *atrophic* and *hypertrophic arthritis* Although there is no specific effect it is believed by many clinicians that ultraviolet irradiation is of value particularly when there is an associated secondary anemia or when the patient has been confined to bed for a long period

It has been claimed that ultraviolet irradiation tends to counteract the decalcifying process in the bones and to have an accessory nutritional influence in managing the anemia debility and allied conditions so frequently found in chronic infectious arthritis It has been pointed out however that chronic infectious arthritis can continue as a progressive crippling disease even in the Arizona desert unless therapeutic measures other than sunlight and climate are utilized

It has been recommended that for chronic infectious arthritis of children reasonable exposure to sunlight or to quartz lights be utilized during the winter months Ultraviolet irradiation has been recommended especially in the treatment of *psoriatic arthritis* A combination of crude coal tar ointment and ultraviolet irradiations is applied to the psoriatic lesions and heat massage and exercise are applied locally to the involved joints (see also treatment of psoriasis in the latter part of this section under the subheading *Diseases of the Skin*)

Diseases of the Genito urinary System — In a series of 26 cases following nephrectomy for *renal tuberculosis* ultraviolet irradiation proved to be a most helpful therapeutic measure for the cure of the tuberculous sinuses and visceral ulceration incident to the disease It has been said likewise that in tuberculosis of the genito urinary tract surgical treatment frequently offers prompt relief if combined with postoperative heliotherapy

Direct irradiation of the bladder for the treatment of *tuberculous ulceration* or *cystitis* has been recommended by a number of observers

Diseases of the Eye — Following a study of eighteen years duration ultraviolet irradiation was reported to have proved its worth in the treatment of diseases of the eye Such treatments for example had reduced the proportion of losses in *ulcus serpens* from 30 to 6 per cent Ultraviolet irradiations likewise had produced favorable results in other *diseases of the cornea conjunctiva* and *sclera* Excellent results have been reported in the treatment of corneal ulcers by accurately localized ultraviolet irradiation

Ultraviolet radiation often is of benefit in the treatment of *tuberculous lesions of the eye* A study of the combined use of local and general ultraviolet irradiation for the treatment of tuberculous lesions of the eye in 100 children revealed some improvement in every case

Diseases of the Ear — It has been claimed that irradiation by means of a Kromayer lamp with a small quartz rod in many instances will abort *furunculosis of the external auditory canal* Combined local and general ultraviolet irradiations have been reported to be of definite value in the treatment of *tuberculosis of the middle ear*

There is little evidence that ultraviolet radiation is of value in the treatment of *chronic otorrhea* for which it occasionally has been recommended it has been pointed out that even a thin layer of mucus or pus will filter out the ultraviolet rays and prevent any favorable action

Diseases of the Nose — Ultraviolet irradiation has been recommended as an adjunct to the surgical removal of *tuberculous lesions of the nose* It likewise has been said that ultraviolet irradiation is of value in the treatment of *infected wounds* and of certain *nasal dermatoses* and its use has been suggested for *ulcerations of the nose* especially septal ulcers Ultraviolet rays likewise have been said to be of value in the treatment of *lupus* of the nasal mucosa

Diseases of the Throat — Combined general and local ultraviolet irradiation has been recommended in the treatment of *tuberculous laryngitis* Strandberg[10] reported a series of 203 cases of tuberculous laryngitis in which treatment with general ultraviolet irradiation was followed by cauterization One hundred and thirteen patients were reported as cured of the disease of the larynx and the majority of the others were said to have improved Thomson[11] challenged these results and said that 32 patients who had pulmonary tuberculosis had been treated according to the Finsen plan without any striking evidence of benefit In only two or three of these cases could some improvement be claimed

Stevenson[1] observed 320 cases of tuberculous laryngitis Thirty eight

of the patients obtained clinical cure 101 were improved 81 were unimproved 59 were worse and 41 had died All of Stevenson s patients received routine sanitorium care vocal rest and various local applications to the throat as well as ultraviolet irradiation It is impossible therefore to say which was the most important factor in treatment

In a study of 452 cases of pulmonary tuberculosis tuberculous laryngitis was present in 19 2 per cent of the cases It was felt that reflected sunlight was of value occasionally in supervised cases particularly during the early stages It would seem that in tuberculous laryngitis general and local ultraviolet irradiation in conjunction with routine care may be of some value in selected cases and certainly is worthy of trial Several observers have felt that the local applications of ultraviolet light were a valuable adjunct

Diseases of the Skin — In no phase of ultraviolet therapy have there been more irrational and hyperenthusiastic claims than in that dealing with treatment for cutaneous diseases In a bewildering mass of hastily written literature concerning ultraviolet therapy claims are made that this physical agent will cure almost any cutaneous disease from acne to zoster[13]

It has been stated[14] that among the diseases of the skin ultraviolet irradiation acts specifically only on *lupus vulgaris* and this only when treatment is strictly on the Finsen principle Likewise ultraviolet irradiation may have a favorable action in other dermatoses *scrofuloderma erythema induratum psoriasis pustular folliculitis indolent ulcer furunculosis acne vulgaris angioma serpiginosum parapsoriasis* and *pityriasis rosea*

Ultraviolet irradiation has been recommended for various forms of *acne acne conglobata acne cachecticorum acne varioliformis* and particularly *acne vulgaris* In treatment for acne vulgaris it generally is considered best to produce a second degree erythema of the entire region covered by the lesions this will be followed by desquamation The most satisfactory results are obtained in the early stages of the disease when slight acute inflammation and only a few comedones are present Response to treatment often is slow Proper dietetic management and medication should be used in conjunction with ultraviolet irradiation Patients always should be told to expect severe reddening of the skin from the second degree erythemal dose which is to be administered They frequently object to heavy doses of ultraviolet radiation on the face which is a common site of the lesions In persistent cases of acne vulgaris it is said irradiation with a cold quartz lamp often frees the patient from the lesions and lessens the degree of scarring In local treatment

for acne vulgaris particularly of the juvenile type ultraviolet irradiation in erythemal doses which produces exfoliation may be used to advantage in conjunction with other measures It is indicated especially for patients ten to fourteen years of age before complete development of adolescence at which time roentgen therapy is contraindicated It has been said that, although roentgen rays undoubtedly are best in local treatment for acne vulgaris their improper use often is followed by disastrous results Ultraviolet light applied locally in combination with astringent lotions is helpful in certain cases

In treatment of *adenoma sebaceum* the use of blistering doses of ultraviolet irradiation has been recommended and it has been said to be useful occasionally for this purpose Erythema of second or third degree must be produced which will be followed by marked desquamation

It has been reported that local applications of moderate doses of ultraviolet radiation may improve the lesions of *angioma serpiginosum* Satisfactory results have been reported in treatment by means of ultraviolet irradiation for *infected granulating regions* following extensive burns in preparation for Thiersch grafts It was said that the effect of such rays on these wounds might be attributed to the following factors (1) a bactericidal effect on the organisms on the surface (2) production of active hyperemia which increased nutrition and resistance of tissues locally and (3) perhaps a stimulation of cell growth

In regard to treatment for *cicatrices* heavy doses of ultraviolet radiation may be found serviceable in the removal of small pitted scars particularly the type encountered following acne

Many authors have reported favorable effects from treatment for *erysipelas* by means of ultraviolet irradiation Excellent results were reported by one investigator who said that each of 91 patients who had erysipelas was given a single simple ultraviolet treatment which was inexpensive and without danger The results were believed to be as satisfactory as those to be obtained from the use of antitoxin roentgen rays or any other accepted method of treatment It is necessary usually to obtain only one heavy dose of erythema of second degree or even third *degree over the entire lesion including 2 inches (5 cm) of* normal skin in every direction around the borders of the lesion The common error in treatment is to give insufficient exposure Fifteen to twenty times the minimal erythemal dose often should be administered Even with smaller doses results may be good Thus one author reported that exposures of only fifteen to sixty seconds at a distance of 20 to 30 inches (51 to 76 cm) to a mercury quartz lamp in 10 cases produced results that were better than those of any other treatment which had been given It was stressed

that treatment should be begun at the earliest possible moment especially before the lesion has had time to extend into the hair or to the external auditory meatus

In a report on 340 cases of erysipelas of all types in which treatment with ultraviolet radiation was employed double the erythemal dose with the hot quartz lamp at a distance of only 8 inches (20 cm) from the lesion or twenty times the erythemal dose with a cold quartz lamp were used Twenty seven patients 7 94 per cent died of erysipelas and 313 recovered The average time between treatment and restoration of normal temperature was 3 9 days The average duration from the time of treatment to the time of dismissal was 8 67 days The average duration from onset to dismissal was 11 34 days It was concluded that ultraviolet irradiation was an effective treatment for erysipelas for consistently good results were obtained in this study which covered a period of seventeen years

The following technic for local application of ultraviolet rays for erysipelas has been suggested The region of involvement and the normal adjacent skin at least 2 inches (5 cm) beyond the border of the lesion should be exposed to ultraviolet radiation A mercury quartz burner may be used The lamp is permitted to run for ten minutes before treatment is begun in order that the lamp may reach its maximal efficiency The rays must strike the diseased region and the adjacent skin at right angles to its surface for ten minutes at a distance of 12 inches (30 cm) provided the erythemal dose of the lamp is approximately one minute at that distance For infants and very young children the time of exposure may be reduced to five minutes and occasionally to three minutes If the lesion of erysipelas shows evidence of spreading a second treatment will be required Usually one intense treatment suffices

It has been said that ultraviolet irradiation may be beneficial in treatment for *erythema induratum* Local irradiation also may improve the lesions of *pustular folliculitis* Although it has been said that ultraviolet radiations are of questionable value for *furunculosis* other authorities have believed that such lesions sometimes may be improved by judicious irradiation

Concentrated ultraviolet irradiation undoubtedly is the best local treatment for *lupus vulgaris* The carbon arc light of the Finsen type is said to be more satisfactory than the Kromayer lamp It has been reported that cure was obtained in only 29 per cent of cases when a Kromayer lamp was used and in 90 per cent of cases when a carbon arc lamp was used At the Finsen Institute during a period of ten years treatment was given in 957 cases of lupus vulgaris In 735 of these cure apparently resulted in 75 treatment was still being carried out and in

147 adequate treatment had failed for one reason or another to be accomplished If this latter group is omitted there are 810 cases in which adequate treatment was received and in 735 of these 90 7 per cent the lesions apparently were cured Further study revealed that of the 735 patients who received adequate treatment and apparently were cured 44 showed signs of recurrence later Nevertheless the results were excellent It is felt that ultraviolet irradiation still may be considered the standard form of treatment for lupus vulgaris

The interesting and valuable observation has been made that in cases of lupus vulgaris the tuberculous skin is more pervious to luminous and to ultraviolet radiation than is normal skin The energy penetration becomes relatively greater as the wavelengths grow shorter until at 313 millimicrons the tuberculous skin may be three to six times as pervious as normal skin Thus greater action of the radiant energy on the diseased skin is to be presumed

In cases of *nevus flammeus* port wine mark ultraviolet irradiations may be very useful excellent results may be obtained with the use of an air cooled ultraviolet lamp and thorough going blanching may be produced readily *Parapsoriasis* and *pernio* also may be improved by ultraviolet irradiations

In cases of *pityriasis rosea* in conjunction with the use of soothing lotions such as calamine lotion or mild protective ointments such as boric acid zinc oxide or 2 per cent sulfur ointment ultraviolet irradiation may be used routinely However ointments and oily applications sometimes may aggravate the condition and calamine lotion without phenol is said to be by great odds the best local application It has been suggested also that erythemal doses of ultraviolet radiation from either cold quartz or hot quartz lamps are too irritating and are unnecessary However divided suberythemal doses are recommended and they usually quiet the itching and promote exfoliation of the lesions within two or three weeks Although previously I have recommended the production of a second degree erythema in order to obtain desquamation I now feel that the suberythemal doses are more satisfactory As I pointed out previously after the use of a second degree erythema the itching fawn colored lesions on the trunk are replaced by generalized sunburn Because the disease is self limited and because the discomfort from the sunburn is considerable it might be preferable to use other palliative measures and permit the disease to run its course By using suberythemal doses recovery may be hastened without producing any discomfort to the patient this procedure is advocated as an adjunct to other forms of treatment

Although it has been reported that ultraviolet irradiation may cause improvement or may be injurious in cases of *psoriasis* nevertheless with judicious applications ultraviolet radiation may be very beneficial If the affected skin is covered with a thin film of crude coal tar ointment and then irradiated with ultraviolet light better results can be obtained than by the use of either one of these agents alone The ointment should consist of gr 30 (2 gm) each of crude coal tar and pulverized zinc oxide mixed with 2 ounces (56 7 gm) each of corn starch and petrolatum

The ointment is applied to the patches for twenty four hours and then is removed with olive oil Vigorous efforts at cleansing are postponed until after the lesions have been exposed to a mercury quartz ultraviolet lamp Thus a thin film of the ointment remains on the lesion during irradiation Only after ultraviolet irradiation may the patient take a bath with soap and water or oatmeal and soda which by aiding in the removal of the remaining débris enhances the effect of the tar and light The light usually is applied at a distance of 30 inches (75 cm) for one minute the time being increased one minute daily for three or four days If the patient then shows no signs of reaction the time of irradiation is increased rapidly and the distance between the lamp and the lesion is decreased

An effort is made to avoid any marked cutaneous reaction but an attempt is made to produce tanning as soon as possible If the therapist is acquainted thoroughly with the effectiveness of his lamp and if he handles it deftly it should be possible to remove all patches of psoriasis in practically all cases in from three to four weeks

Patients who have psoriasis are likely to experience the development of arthritis In a series of 936 cases of psoriasis studied at the Mayo Clinic arthritis was associated with 133 14 per cent of them In 40 of these 133 cases systematic treatment with tar and ultraviolet irradiation was given The eruption responded as readily in these cases as in those in which arthritis was not present It was a striking fact that in about half of these cases the active symptoms of the arthritis entirely disappeared without any other treatment

Employed judiciously a combination of local and general ultraviolet irradiation may be of benefit to *scrofuloderma* There is sufficient evidence to justify the statement that ultraviolet irradiation is of value for certain types of cutaneous tuberculosis scrofuloderma

Indolent ulcers occasionally may be caused to heal more rapidly by the use of erythemal doses of ultraviolet radiation or by daily exposures to graduated doses of solar radiation In regard to wounds particularly *indolent wounds* the use of unaltered sunlight has been recommended

highly I have been able to obtain what I consider to be comparable results by exposing the indolent wound first to a radiant heat lamp and then to a mercury quartz lamp

There is a difference of opinion regarding the value of ultraviolet irradiation for about thirty additional dermatoses

Miscellaneous Diseases — In *rickets* it is believed that ultraviolet irradiation furthers the absorption from the intestine of either phosphorus or calcium or both It is probable that the hydrogen ion concentration is the limiting factor in such action A number of investigators have shown that to produce beneficial effects in the treatment of rickets it is necessary to administer only comparatively small doses of effective ultraviolet radiation

For example a single weekly exposure to one erythemal dose of ultraviolet rays was sufficient to produce healing of rachitic lesions of infants Irradiations from a mercury quartz lamp front and back for four to five minutes once weekly until approximately 100 minutes of exposure had been given was sufficient to effect cure in a series of 43 rachitic nurslings so treated

Heavy doses of ultraviolet light did not prevent rickets in rats which had been placed on a rickets producing diet provided they were prevented from licking their fur or eating their excretions If however the rats were shaved the skin sterol then was activated by irradiation absorbed and exerted antirachitic effects

It has been shown that the provitamins D exhibit pronounced ultraviolet absorption Of the eight to ten provitamins D which are said to exist only two ergosterol and 7 dehydrocholesterol appear to be very common When irradiated these provitamins become extremely active and 5 mgm of either is equivalent in potency to 1 liter of good cod liver oil Direct irradiation of the skin by ultraviolet rays may be specific in the treatment of rickets

Results comparable to those obtained in the treatment of rickets may be obtained also by the use of ultraviolet irradiation in cases of *tetany* and *spasmophilia*

Among the *unusual uses of ultraviolet irradiation* may be mentioned its employment for diagnostic purposes for the identification marking of newborn infants for the purpose of producing hardening of the nipples prenatally and for the sterilization of air in operating rooms It has been pointed out that prenatal irradiation and the irradiation of the nursing mother are efficacious in the prevention of rickets in the child and that direct irradiation of cows will impart an antirachitic potency to their milk

Contraindications to the Application of Ultraviolet Radiant Energy

Ultraviolet irradiation is contraindicated in the presence of cardiac insufficiency valvular heart disease advanced myocarditis arteriosclerosis nephritis advanced bilateral renal tuberculosis with impending uremia and pulmonary tuberculosis of the advancing exudative type

It sometimes is contended that previous exposure to roentgen rays contraindicates subsequent exposure to ultraviolet radiation The idea probably arises from the fear of a possible cumulative action produced by the latent erythema from the roentgen rays added to the erythema from the ultraviolet rays With this exception there is no apparent contraindication to combining the two procedures Recently Ellis and Kirby Smith[15] studied 11 patients who had been given from 10 to 16 one third erythemal doses of roentgen rays and from 4 to 20 erythemal doses of ultraviolet rays None showed any evidence of roentgen ray dermatitis They concluded that roentgen therapy has simply an additional action separate from the effect of the ultraviolet radiation on the skin For example if R represents the permanent or late effect of the roentgen rays and A the permanent actinic cutaneous change then the total late changes will equal R plus A When roentgen (R) and ultraviolet irradiations (A) are given simultaneously alternately or later neither exerts a beneficial or deleterious effect on the other but there is only a summation of the effect of one plus that of the other

Ultraviolet irradiation may cause an exacerbation provoke an attack or produce other injurious effects in such cutaneous lesions as eczema lupus erythematosus herpes simplex erythema solare perstans xeroderma pigmentosum freckles atrophy keratoses and permaturely senile skin

Exposures to ultraviolet radiation should not be employed for tuberculosis of the suprarenal glands or for certain types of tracheobronchial adenitis Such exposures are contraindicated also in the presence of hyperthyroidism and diabetes because pruritus and heightened irritability may result Still other contraindications to the use of ultraviolet irradiation are advanced cachexia inanition extreme age and acute forms of generalized dermatitis

Summary of Data on Radiant Energy

Ultraviolet irradiation has been used extensively but indiscriminately in the *practice of medicine* However *in a rather large number of con*ditions the evidence indicates that ultraviolet irradiation is or gives

promise of being valuable Among these conditions may be mentioned tuberculous peritonitis and enteritis calcium deficiency diseases secondary anemia carbon monoxide poisoning pulmonary tuberculosis tuberculosis of bones and joints atrophic and hypertrophic arthritis tuberculosis of the genito urinary tract ulcus serpens corneal ulcer tuberculous lesions of the eye ear or nose nasal ulcerations tuberculous laryngitis certain cutaneous diseases, rickets, tetany and spasmophilia

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HYDROTHERAPY

Although it is one of the oldest forms of therapy and one which often can be employed to advantage hydrotherapy has been neglected recently Interest in the employment of water for therapeutic purposes has waxed and waned throughout the centuries but never has ceased entirely Baruch[1] said Of all remedial agents in use since the dawn of medicine water is the only one that has survived all the vicissitudes of doctrinal changes because its rise or fall was always contemporaneous with the rise and fall of intelligence among medical men If this is true we modern physicians should look to our laurels and inquire into the present state of our collective intelligence The current medical literature is woefully lacking in careful scientific evaluations of the various phases of hydrotherapy

It has been said Hydrotherapy includes the application of water in any form from the solid and fluid to vapor from ice to steam internally and externally Water can be applied either locally or generally

Methods of Applying Hydrotherapy

Local Application —Among the methods of applying water locally for therapeutic purposes can be mentioned local baths sitz baths contrast baths whirlpool baths local douches irrigations and compresses

Local Baths The arm hand leg foot or other local region of the body can be immersed in water at different temperatures to cause local effects which usually are of a thermal or mechanical nature Baths for the extremities usually are administered in specially shaped containers which conform to the shape of the limb A large oval dishpan can be used for the arm and a large bucket or tub for the leg In the so-called half bath only the pelvis hips and lower extremities are immersed in water contained in an ordinary bath tub

In the *sitz (hip) bath* the patient sits in water with only the hips pelvis and external genitalia immersed In institutions special tubs are employed for administration of these baths but in the home a wash tub can be substituted

Alternate applications of hot and cold water *contrast baths* to the extremities are very useful in treatment for hypertrophic arthritis and for certain circulatory diseases The usual plan of alternately immersing the part in hot and then in cold water for intervals of one minute is not so satisfactory as are immersions for longer period of time Woodmansey and his associates in England found the best circulatory responses when

the hot water was applied for six minutes and the cold water for four minutes Our American patients possibly because they are accustomed to warmer houses dislike the more prolonged periods of cold

Checking the work of Woodmansey I found that patients in this country responded best to a routine which employed either five minutes of heat and two minutes of cold or four minutes of heat and one minute of cold To obtain the best vascular response the patient always should start and end with the hot water The cold water should be kept at a temperature of 50° to 65° F (10° to 18 3° C) and the hot water at 100 to 110° F (37 8° to 43 3° C) If the first routine is employed the treatment should last for either 19 or 26 minutes thus 5–2–5–2–5 or 5–2–5–2–5–2–5 If the latter procedure is employed treatments will require 19 or 24 minutes thus 4–1–4–1–4–1–4 or 4–1–4–1–4–1–4–1–4

Baths of whirling aerated water *whirlpool baths* at a temperature of *110° F (43 3° C) have been employed extensively in civilian hospitals* for increasing the peripheral circulation of the extremities These baths which were developed during the World War of 1914–1918 still are considered to be extremely useful especially in the management of fractures of the extremities Specifications for the construction of a simple ' home made whirlpool bath are illustrated in Fig 23 For institutional work specially shaped whirlpool baths are available for immersion of the leg there is another type which is raised on a pedestal for immersion of the arm Portable whirlpool baths also are available These contain an immersion heater and a mechanical electrically operated device for agitating and aerating the water

Various *sprays* and *douches* can be employed therapeutically The ordinary bath spray sometimes called a rose spray can be used to shower a local region with hot or cold water or it can be employed to administer contrast baths to regions such as a shoulder which cannot be immersed readily in a tub

The *jet douche* is a stream of water projected from an ordinary hose nozzle If the water from such a nozzle is spread in the shape of a fan by placing a finger over the opening it is called a *fan douche* If the circular aperture in the nozzle is extremely small so that a very fine forceful stream of water is projected on the body it is spoken of as a *filiform douche* Such a stream may be sufficiently forceful to destroy surface epithelium and even to cause bleeding

Irrigations are used chiefly for flushing of various bodily cavities that is the colon vagina ear, nose throat urinary bladder or stomach In the few instances in which irrigation of the colon is necessary the physician can employ an ordinary bed a plain glass irrigation jar on a

stand a rectal tube (no 34 French) a Y tube with two clamps and a large closed jar to receive the return flow This simple equipment is equally as effectual as the elaborate colonic irrigation tables covered with chrome metal and fancy gadgets which so frequently are marketed for this purpose

For irrigation of the vagina the usual irrigation can or fountain syringe

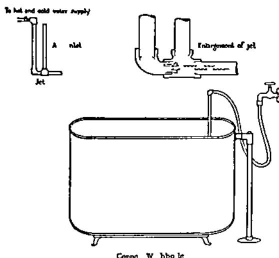


FIG 23 Specifications for the construction of a home made whirlpool bath (Courtesy of the Council on Physical Therapy of the American Medical Association)

with a hard rubber tip which is sufficiently large to prevent its passage into the cervical canal can be employed

For irrigation of the ear nose or throat the usual irrigation can or rubber bag and tubing can be employed A very satisfactory irrigation tip can be made by inserting the glass portion of an ordinary eye dropper into the end of the tubing Irrigation of the bladder is performed by connecting the fountain syringe to an ordinary urethral catheter

Finally irrigation of the stomach can be accomplished by the employment of one of several types of tubes The large rubber stomach tube which varies in caliber from no 12 to no 30 French can be used Or a

large no 30 French, Boas tube a nasal catheter with a soft rubber tip or a small caliber Rehfuss tube with a metal tip can be employed Fluids can be introduced through a funnel or by means of a syringe and can be removed by siphonage or by means of the syringe

Cloths partially wrung out after dipping in hot or cold water can be applied to some region of the body to produce a local circulatory reaction These are spoken of as *compresses* or *packs*

General Application — Among the methods for the general application of water can be mentioned baths including full baths brine baths effervescent baths and bland baths Hubbard tanks pools showers douches and packs

A cold plunge in a *full bath* at a temperature of 50° F (10° C) occasionally is employed as a powerful excitant The tepid full bath at temperatures between 80° and 92° F (26 7° and 33 3° C) sometimes is used therapeutically A neutral bath is one which is kept at a temperature of from 92° to 97° F (33 3° to 36 1° C) while the hot bath is applied at temperatures between 98° and 108° F (36 7° and 42 2° C) *Continuous full baths* sometimes are employed They are kept at neutral temperature and the patient lies on a canvas hammock which is beneath the water in a large tub

The chief advantage of the *brine bath* is its buoyancy It usually contains from 5 to 30 pounds 2 3 to 13 6 kg of sodium chloride to 40 gallons 160 liters of water Little salt is absorbed through the skin It is employed usually for administration of certain types of underwater exercise

Baths containing carbonated water *effervescent baths* commonly known as carbon dioxide or Nauheim baths occasionally are employed in treatment of certain types of cardiac disease Usually ½ pound 0 2 kg of sodium bicarbonate is placed in a tubful of salt water Then six or eight large tablets of specially prepared acid sodium sulfate are arranged along the floor of the tub A chemical reaction follows which causes the liberation in the water of large quantities of carbon dioxide The patient then is immersed in this bath

Sometimes oxygen is bubbled into a tub of water through rattan reeds to provide an oxygen bath This type of effervescent bath was recommended by Nylin[3]

Sometimes soothing or *bland baths* are used in treatment of certain acute inflammations of the skin They usually are kept at neutral temperature and soothing medication is added to the water A suitable bland bath can be prepared by adding to the full neutral temperature bath a decoction consisting of 5 pounds (2 3 kg) of starch in 1 gallon

(4 liters) of water or 3 pounds (1 4 kg) of wheat bran in the same amount of water

In order that underwater exercises can be administered easily a special butterfly shaped tank has been constructed This kind of tank usually called a *Hubbard tank* now is employed extensively in the various hospitals of the United States A simple type can be constructed for home use specifications are obtainable from the Council on Physical Therapy of the American Medical Association

Therapeutic pools have been developed to a high degree of efficiency They are employed extensively for underwater exercises and can be found in many large hospitals schools for crippled children and orthopedic institutions

The overhead *shower bath* often called a *rain douche* and the *needle shower* sometimes are employed therapeutically The latter is composed of semicircles of shower heads which spray many fine forceful streams of water onto the surface of the body The pressure of the water causes the needle like streamlets to sting the skin hence the designation needle shower

If the surface of the body is sprayed alternately by forceful jets of hot and cold water the procedure is called a *Scotch douche* This treatment when properly applied by a skillful individual has a distinctly invigorating and refreshing effect

The *full wet pack* the *blanket pack* and the *towel pack* all have been employed therapeutically In each the patient is wrapped in cold or hot moist coverings Usually the patient is wrapped in a cold wet covering and then quickly enveloped in warm coverings A reactive hyperemia occurs and he soon feels warm and begins to perspire As the patient remains in the pack it finally begins to produce a distinctly sedative effect

Physical Principles Concerned in the Employment of Hydrotherapy

Water solidifies at 32 F (0 C) as ice it can be applied locally Water occasionally is applied locally through a jet in its gaseous form steam However in most instances water is applied in its liquid form when local effects are desired Because of this flexibility of application water often is applied generally in solid liquid or gaseous form A general application of the solid form is the ice pack of the liquid form the full bath and of the gaseous form the steam bath

Water is an excellent medium for producing by conduction changes in

the temperature of the bodily tissues It is said that it imparts its temperature to bodily tissue more readily than does air at the same temperature A sensation of chilliness will be observed much more rapidly by anyone lying quietly in a tub of still water at 80° F (26 7° C) than by anyone lying in still air at the same temperature Also water has a high specific heat that is a large amount of heat is required to raise its temperature Conversely when it cools it liberates a large amount of heat to substances with which it is in contact Therefore water is a very satisfactory means of applying conductive heat

Hydrotherapeutic procedures can cause mechanical as well as thermal effects *The impact of water applied under pressure to the skin will tend* to have a stimulating effect on the sensory nerve endings A shower bath generally is considered to be more stimulating and refreshing than a tub bath

Action and Uses of Hydrotherapy

With regard to the local effects of hydrotherapy one of the most interesting of the recent observations is that of Blair[4] His studies on the physiological effects of alternate increase and decrease of the blood supply may aid in explaining the value of contrast baths in the treatment of fractures Furthermore Blair s observations may explain in part the reason for the varied opinions concerning the effect of hyperemia on calcification of bone *He concluded that it was the alternate* increase and decrease in the volume of blood which promoted calcification of bone whereas prolonged hyperemia produced decalcification of bone and prolonged ischemia caused calcium deposition and ossification

Normally the volume of blood reaching the bones of the extremities is varied by the alternate contraction and relaxation of muscles which take place during the usual activity of the part Following a fracture prolonged immobilization prevents this activity Blair concluded that contrast baths which have been used for years to hasten healing of fractures probably caused an alternation of blood supply to the part and were advantageous because alternating ischemia and hyperemia maintain normal calcification of bone If Blair s observations are correct then contrast baths followed by massage and muscle setting exercises alternate static contraction and relaxation of muscles should be particularly effective in promoting healing and calcification of fractures

It has been pointed out by McClellan[5] that hydrotherapeutic procedures cause chiefly thermal and mechanical stimulation This stimulation acts as an irritant to the sensory nerve endings and may produce a re

sponse locally by reflex action The local reaction to cold water is contraction of elastic and muscular fibers in the cutaneous and subcutaneous regions which results in ischemia When the application of cold ceases the fibers relax with the result that hyperemia occurs Hot applications tend to result in an atonic reaction and cold applications in a tonic reaction

The chief effect of generalized application of water is thermal The bodily temperature will tend to rise or fall according to the temperature of the bath The physiological effects of general exposure to heat or to cold already have been discussed in the sections dealing with applications of heat and cold

Most writers on hydrotherapy stress the importance of obtaining a good reaction The action caused by brief applications of cold water consists of peripheral vasoconstriction pallor chilliness shivering and increases in respiratory and pulse rates The reaction which starts immediately and lasts for about twenty minutes consists of peripheral vasodilatation redness of the skin warmth relaxation and slowing of the respiratory and pulse rates Likewise a reaction may be noted following a brief application of hot water This reaction has been said[6] to consist of muscular relaxation lowered arterial tension and increase in the pulse rate with shallow respirations In order to produce a marked hyperemia alternate applications of hot and cold water often are recommended

Cold baths increase the general metabolic rate and the amount of oxygen inspired Hot baths also will increase the metabolic rate if they are administered for a period which is sufficiently long to raise the systemic temperature but the amount of oxygen which is inspired will be decreased

Local Application — Warm or hot *local baths* are applied to the upper or to the lower extremity in treatment of arthritis burns cellulitis circulatory diseases contusions sprains and infected wounds Cold foot baths have been recommended in treatment of bromidrosis and for persistent coldness of the feet Cold sitz baths have been recommended in treatment of such conditions as amenorrhea prostatorrhea atony of the bladder atonic constipation and sexual impotence The hot sitz baths have been suggested in treatment of dysmenorrhea amenorrhea prostatitis tenesmus ureteral colic pelvic inflammation and gluteal fibrositis

Contrast baths are especially useful in treatment of hypertrophic arthritis of the hands and feet and in the management of fractures sprains and contusions Such baths have been employed also for peripheral vascular disease

In the auxiliary treatment of fractures of the extremities after removal of dressings whirlpool baths often are valuable This type of bath improves circulation relaxes muscles and seems to have a sedative effect thus preparing the part for subsequent massage and exercise Indications for use of whirlpool baths are much the same as those for the contrast baths Whirlpool baths too are used in treatment of traumatic lesions such as sprains contusions dislocations and of arthritis peripheral vascular diseases and infected wounds of the extremities

Warm or hot *irrigations* of the ear nose or throat are employed to relieve inflammation and to remove exudate in the presence of such conditions as otitis media furunculosis of the external auditory canal chronic rhinitis, acute nasopharyngitis or peritonsillar abscess

Irrigations of the stomach are used for relief of gastric retention in association with pyloric stenosis or carcinoma They have been employed also to remove recently ingested poisons Vaginal irrigations often are indicated in the management of leucorrhea vaginitis endocervicitis endometritis and pelvic inflammatory disease

There are very few indications for the use of *colonic irrigations* It is possible that they may be useful occasionally for removal of masses of impacted feces from the lower part of the bowel Such irrigations should not be employed routinely Even occasional irrigations rarely are indicated

Hot *compresses* are employed at times in treatment of muscular spasm or of acute inflammatory processes Cold compresses sometimes are applied over the precordium in treatment of tachycardia and cardiac neurosis

General Application — The *cold full bath* has been recommended to improve functional activity to stimulate general metabolism and to combat the debility associated with sedentary living It was recommended by Brand in treatment of typhoid fever The *tepid bath* has been employed chiefly as a sedative or to combat excessive febrile reactions *Neutral baths* are used occasionally to treat insomnia or to allay nervous excitability *Warm baths* have been used for convulsions of infancy to diminish the cerebral manifestations of certain acute febrile disorders and to treat such conditions as acute sciatica dysmenorrhea amenorrhea and insomnia *Hot baths* often may be employed to advantage in controlling acute exacerbations of chronic atrophic arthritis as well as for fibrositis myositis neuritis muscular spasm and abdominal cramps *Continuous baths* are used particularly in the control of acute manias They have been employed also in treatment of extensive burns indolent ulcers cutaneous diseases suppurating wounds and large ab

scesses *Brine baths* have been used especially for arthritis fractures dislocations fibrositis myositis and osteomyelitis

Effervescent baths have been used for cardiac disease especially for valvular or myocardial lesions The oxygen bath has been recommended for hypertension and cardiac neurosis and as a mild sedative for advanced cardiac disease *Bland baths* are used to relieve generalized pruritus and dermatitis

Underwater exercises in tanks or pools are employed chiefly for poliomyelitis spastic paralysis and certain orthopedic and neurological conditions *Douches* and *showers* are employed to improve peripheral circulation and to act as general stimulants Neurasthenics and debilitated individuals often are benefited by the Scotch douche *Packs* can be used to advantage in home treatment of arthritis fibrositis or myositis as well as for control of delirium psychosis hyperexcitability and insomnia

Contraindications to the Employment of Hydrotherapy

Very hot or very cold sitz baths should not be administered during pregnancy or the menstrual period Cold local baths or extremely hot baths at a temperature higher than 105° F (40 6° C) are not to be used in the presence of advanced peripheral vascular disease The former aggravate the condition and the latter may cause burns which would heal slowly if at all

In irrigation of the nose the force of the stream must not be too great or else infected material may be carried into the eustachian tube or the nasal accessory sinuses In irrigating the throat if the stream of fluid is directed on the soft palate or uvula it may cause gagging Irrigation of the stomach should not be employed to remove corrosive poisons because the pressure of the fluid may cause perforation of the eroded wall of the stomach

Routine daily irrigations of the vagina are potentially harmful because they may remove the normally germicidal vaginal secretions Colonic irrigations may increase rectal discharges irritate the anus disturb a chronic ulcer of the bowel produce nausea or cause fatal intussusception or volvulus It has been reported that they may cause also rectal bleeding from hemorrhoids a fissure or an ulcer or cause a torn rectal valve In one instance perforation by the rectal tube of a diverticulum of the sigmoid has been reported

Cold compresses should not be used in the presence of impaired circulation sensitivity to cold or asthenia Hot compresses should be

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employed with caution for peripheral vascular disease because of the danger of burns with their disastrous consequences

General cold baths should not be used, if there is hypersensitivity to cold because collapse may occur Urticaria also may be produced by cold baths The cold bath should not be employed in the presence of arteriosclerosis nephritis spastic paralysis nervous irritability or cardiac weakness Neutral baths are contraindicated if the patient has hypotension or a subnormal bodily temperature Hot baths are not to be employed in the presence of marked hypertension advanced debility functional neurosis or conditions in which hemorrhage impends

Among the dangers of continuous baths have been mentioned heat prostration chilling scalding convulsions and drowning Continuous baths should not be employed in the presence of cardiac disease hypotension or asthenia Carbon dioxide baths should not be used for patients who have marked cardiac decompensation congestive heart failure or advanced syphilitic heart disease

Underwater exercises are contraindicated for acute infections or febrile diseases acute inflammations of joints acute neuritis tuberculosis of joints and during the acute painful stage of early poliomyelitis General packs should not be employed when there is severe circulatory disturbance advanced cardiac disease or extreme exhaustion or when it is evident that a reaction may not occur

Summary of Data on Hydrotherapy

Many local and general hydrotherapeutic procedures are simple of application and can be employed with ease in the patient s home Physicians often have neglected to use these effective procedures, probably because they are not taught properly in our medical schools

There is little room to doubt the efficacy of contrast baths whirlpool baths irrigations hot tub baths underwater exercises and packs in the management of certain pathological conditions These procedures should be employed more extensively in general practice

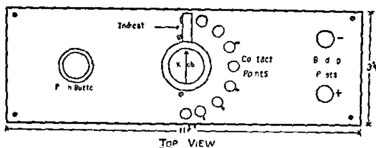
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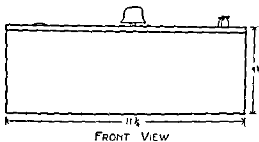
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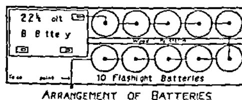
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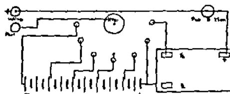


Fig 24 Specifications for the construction of a constant galvanic current generator of low cost (Courtesy of the Council on Physical Therapy of the American Medical Association)

ELECTROTHERAPY

The types of electrical current commonly employed in modern medical practice are the constant current the faradic current the various sinusoidal currents and the high frequency or diathermy currents

The Constant Current

The constant or galvanic current is a unidirectional current of low voltage (tension) and amperage (volume) The current possesses polarity there being a positive and a negative pole The current is capable of producing migration of ions it can be used in medicine to deposit ions of certain salts on or in the superficial layers of the skin or mucous membranes If these ions are concentrated in a small region destructive chemical effects of a caustic nature can be obtained

The constant current is employed therapeutically chiefly for electrolysis particularly for epilation and for common ion transfer iontophoresis of a few medicinal ions The Council on Physical Therapy of the American Medical Association[1] has said that the interrupted low frequency current and the constant electric current are widely used in medical practice and are unquestionably of value in the treatment of a limited number of conditions

Methods of Applying the Constant Current

The constant current can be derived from a battery of electrical cells which usually are connected in series or from the main supply current if this is of the direct (D C) rather than of the alternating (A C) variety If the latter is used a shunt resistance is placed in the patient s circuit to reduce the amount of current

In the United States the house current usually is of the alternating (A C) variety this can be employed as an indirect source of the therapeutic constant current only by the introduction of a *motor generator* a rectifier or a B battery eliminator between the house outlet and the patient

The chief advantages of a therapeutic device which derives its constant current from a battery of dry cells are that it is portable and that it is not dependent on any outside electrical circuit The specifications for construction of a simple low cost constant current generator have been prepared by the Council on Physical Therapy of the American Medical Association (Fig 24)

but the ions can be absorbed into the circulation from the superficial layers of the skin and thus produce distinct local and even systemic effects

Electrolysis achieved by sharp localization of caustic products at the tip of a needle is a suitable method for obtaining destruction of certain lesions of the skin and mucous membranes The indications for electrolysis are comparatively few In many instances the newer and more readily controlled high frequency currents are used for destruction of small superficial lesions There are however several conditions for which electrolysis still is considered the method of choice Both MacKee and Cipollaro[3] recommended electrolysis for destruction of certain cutaneous lesions such as adenoma sebaceum dilated capillaries benign cystic epitheliomas hemangiomas hydrocystomas hypertrichosis keratosis pigmented hairy moles spider nevi and syringocystadenomas By far the most common and important indication for electrolysis is hypertrichosis As Cipollaro[3] stated It is the only method for permanent and safe removal of unwanted hairs

For selected cases of chronic otorrhea Friel[4] has recommended the employment of *zinc iontophoresis* Lierle and Sage were not impressed so favorably with the procedure and Hollender[5] concluded that although the method may be useful in selected cases the evidence presented to date is insufficient to place the procedure on a firm scientific basis Recently zinc iontophoresis has been recommended in treatment of hay fever and rhinitis The method may cause fibrosis of the nasal submucosa without damage to the superficial epithelium Local application of phenol can produce a similar effect At best the procedure is palliative and not curative It has seemed to be more effective in non allergic rhinitis than in seasonal hay fever Its value and dangers as yet have not been determined fully

Kovacs[7] has recommended the employment of *iontophoresis of mecholyl* acetyl beta methylcholine chloride in treatment of varicose ulcers *Zinc* or *copper iontophoresis* has been employed in the past for indolent ulcers

Kling[8] advocated the use of *histamine iontophoresis* in treatment of peripheral circulatory diseases He was of the opinion that the procedure was more effective than were inunctions of histamine Neither procedure is particularly effective in peripheral vascular diseases I have tried histamine iontophoresis and could see no advantage over other simpler methods of producing hyperemia

Several authors[8, 9, 10, 11] have urged strongly the use of iontophoresis of histamine or of mecholyl (acetyl beta methylcholine chloride) in treatment of atrophic hypertrophic or traumatic arthritis It was thought that

Physical Principles Concerned in the Therapeutic Application of the Constant Current

Certain substances when dissolved in water form a solution that possesses an osmotic pressure greater than that of water Such a solution will conduct a constant current The molecules are decomposed by the current and their components collect at either the positive or the negative pole of the current Acids bases and salts are included among the substances which act in this manner They are called 'electrolytes and the smaller particles into which they are decomposed are called ions

When the constant current is passed through an aqueous solution of sodium chloride a migration of ions will occur Some will collect at the positive and others at the negative pole Similarly if the constant current is passed through the bodily tissues a migration and a concentration of their ions will occur beneath the electrodes connected to the two poles of the source of the current The therapeutic effectiveness of the constant current depends on this ability to cause migration of ions

Action and Uses of the Constant Current

When applied diffusely to the skin the constant current because of its stimulating effect on sensory nerve endings will produce reflex vasodilatation However there are other simpler methods of obtaining this effect

When concentrated at the tip of a needle the constant current will cause chemical changes owing to the collection of ions which are so intense that caustic effects are obtained Caustic destruction of the tissues ensues

The ions of certain metals such as copper or zinc and of certain other substances such as histamine hydrochloride and mecholyl acetyl beta methylcholine chloride have been introduced into the superficial layers of the skin or mucous membranes by means of the constant current for therapeutic purposes

The positive pole repels metals and alkaloids into the tissues the negative pole repels acids acid radicals and halogens This should be remembered when attempts are made to introduce these substances into the tissues in order that the correct pole will be employed

When *iontophoresis* is employed the penetration of ions never will be greater than a fraction of a millimeter nevertheless certain valuable superficial effects can be obtained The low velocity of the ions and the low potential at which they are introduced preclude deep penetration

weakened muscles by increasing their circulation He was sufficiently observant to realize however that the procedure was not so effective in strengthening weakened muscles as was voluntary contraction

The faradic current which is employed for therapeutic purposes is an intermittent asymmetrical alternating current obtained from the secondary winding of an induction coil Like the constant current its field of usefulness is distinctly limited At present it is employed chiefly for stimulation of weak or atrophied muscles which have a normal nerve supply for testing for the reaction of degeneration and as a means of suggestion for treatment of hysteria

Methods of Applying the Faradic Current

Small faradic units long have been marketed for medical use Any electrician can build one at small cost by following the directions which have been prepared by the Council on Physical Therapy of the American Medical Association (Fig 25)

This device employs a sliding iron core which permits the current in the secondary coil to be varied smoothly in a surging manner This surging of the current by sliding the core in and out permits the operator to produce rhythmic graduated contractions of muscles through which the current is passed

More elaborate types of the faradic unit dispense with the manual production of variation in the current and employ motor driven cams or other mechanisms to vary its intensity A suitable portable faradic coil which has been employed extensively in England has been developed by Sir Morton Smart[13, 14]

Physical Principles Concerned in the Therapeutic Application of the Faradic Current

The device for production of a faradic current consists of a constant current source such as a battery of electrical cells an induction coil and a current interrupter The primary coil of the apparatus consists of a few turns of copper which encircle a core made of a bundle of soft iron wires The secondary coil consists of many turns of fine copper wire which encircle a hollow fiber cylinder This cylinder is made to ensheathe the primary coil Either this cylinder or the iron core is arranged so that it can be slid in or out to vary the amount of induced current in the secondary coil

The asymmetrical current, which flows from the secondary coil will

the procedure caused local vasodilatation within the joint over which it was applied It has been commented that this can be little more than pure conjecture' I have found little to recommend the procedure and prefer simpler methods of producing vasodilatation in treatment for arthritis

Copper iontophoresis has been employed for many years in treatment for endocervicitis but no one seems to have compared it carefully with other methods of treatment Tovey[1] for example recommended the procedure enthusiastically but presented no statistical or comparative studies to support his views

Contraindications to the Employment of the Constant Current

Following iontophoresis of either histamine or mecholyl (acetyl beta methylcholine chloride) untoward systemic reactions may occur which must be guarded against When electrolysis is performed care should be taken to avoid application of the current from the positive pole through a steel needle, or else a tattoo may result Incorrect technic in electrolysis may cause painful disfiguring or even dangerous lesions Infections keloids or regions of depigmentation may occur Incomplete destruction of a benign melanoma may cause it to become malignant

Use of excessive amounts of current in copper iontophoresis of the cervix may produce sloughing and subsequent stenosis of the cervical canal Improper employment of zinc iontophoresis in the nose may result in impairment of the sense of smell

Summary of Data on the Constant Current

The constant current is useful chiefly for electrolysis and for iontophoresis Electrolysis is indispensable for safe epilation and can be employed to advantage also for destruction of a few cutaneous lesions

Iontophoresis of certain medicinal ions may be employed occasionally for therapeutic purposes The constant current has a distinct but limited field of usefulness in medicine

The Faradic Current

The therapeutic use of the faradic current followed the discovery by Michael Faraday in 1831 of electromagnetic induction Guillaume Duchenne is believed to have been the first to employ the faradic current in medicine He thought that faradic stimulation aided in the recovery of

Action and Uses of the Faradic Current

The physiological effect of faradic stimulation of muscles is similar to that of other forms of electrical stimulation However the method of accomplishing the muscular contraction differs from that of other currents

The effective phase of the secondary faradic current occurs at the break These break phases occur at a rate of 50 to 100 times per second These break stimuli follow one another so rapidly that the muscle which possesses a normal nerve supply will have no time to relax between stimuli and a smooth even tetanus will result The very short break stimuli lasting 0 001 second although very suitable for stimulating the normal muscle which has a chronaxia of 0 0015 second will not produce any effect on a paralyzed muscle which because of its lack of innervation has a chronaxia of 0 01 to 0 1 second

These facts form the basis for the employment of the faradic current in testing for reaction of degeneration A muscle with an intact normal nerve supply will respond to faradic stimulation whereas if the nerve supply is damaged or degenerated the muscle will not respond The details of the test for reaction of degeneration will not be described here but can be found in other books[15 16]

As has been mentioned the faradic current is employed chiefly for performing this test or for stimulation of muscles which have poor tone but possess a normal nerve supply It is particularly useful in stimulating muscles which have lost tone and have become atrophied following prolonged disuse The current also can be applied by means of a special brush electrode to cause strong painful muscular contractions as a means of inducing suggestion in cases of hysteria Another valuable application of the faradic current is for the purpose of teaching a patient to contract one muscle independently Muscle setting exercises often are valuable but it may be difficult to train a patient to contract the correct muscle or muscles Faradic stimulation of the muscles in question immediately will demonstrate to the patient which muscles are to be contracted Once he feels these muscles contract he may be able to continue the contractions voluntarily The electrical stimulation may save several hours of explanation and practice

Faradic stimulation occasionally can be employed to produce rhythmic contractions of muscles which the patient cannot or will not contract of his own volition Smart[13 14] recommended its employment for many conditions including such as strains muscular atrophy fibrositis tenosynovitis sprains dislocations fractures arthritis and certain forms of paralysis

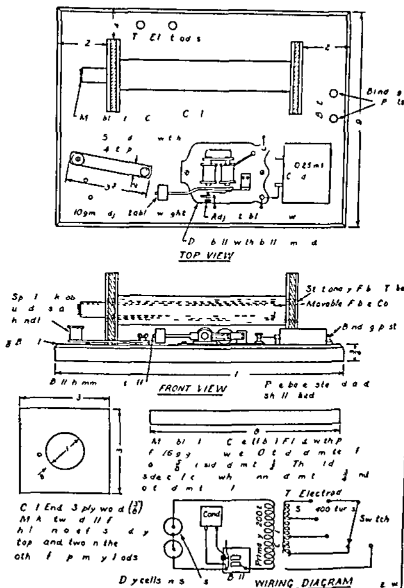


Fig. 25. Specifications for the construction of a simple faradic coil (Courtesy of the Council on Physical Therapy of the American Medical Association)

stimulate contractions of normal muscles but will not cause muscles which have lost their nerve supply, to contract

tetanization of normal skeletal muscles no single stimulus is long enough to produce a contraction in a paralyzed muscle

Modifications of these basic interrupted or waved currents include various types of surging such as the types known as the surging sinusoidal current and the surging sinusoidal current with a sustained peak

When employed for stimulation of muscle the sinusoidal currents are somewhat less unpleasant than is the faradic current because their alternations are perfectly smooth The indications for their use are practically the same as those for the faradic current

Methods of Applying the Interrupted Galvanic and Sinusoidal Currents

The interrupted galvanic current is produced by the apparatus for generation of the constant galvanic current with the exception that some method must be provided for making and breaking the electrical circuit A make and break key or button can be used to permit manual interruption of the current or some mechanical interrupter such as a metronome rotating cam or automatic switch can be employed

To obtain the slow sinusoidal current a source of galvanic current can be employed in conjunction with a variable resistance and current reverser which will wave the current in the form of a sinusoid The rapid sinusoidal current usually is derived from an alternating current main and is modified and protected suitably Elaborate machines which produce the three basic currents variously modified have been marketed

Physical Principles Concerned in the Application of the Interrupted Galvanic and Sinusoidal Currents

The physics of the interrupted galvanic current is the same as that of the constant current The ordinary house current usually is a rapid sinusoidal current of 60 cycles and of such high voltage and amperage that unmodified it cannot be employed for therapeutic purposes If the voltage and amperage are reduced to tolerable volumes then the current can be employed for stimulation of muscles possessing a normal nerve supply

No rate of oscillation ever has been agreed on as the dividing line between rapid and slow sinusoidal currents It has been suggested that if no single wave before reversal of flow lasts longer than 1/50 (0 02) of a second such a sinusoidal current should be called rapid that if the length of time for the completion of one wave is greater than 1/50 (0 02) of a second then the current can be considered to be a slow sinusoidal current

Contraindications to the Use of the Faradic Current

Faradic stimulation is contraindicated in treatment during the acute stage of sprains in which the muscular contractions which it produces might cause further extravasation of blood and lymph into the tissue spaces and might interfere with normal repair. Stimulation of muscles by the faradic current should be used with caution in recent fractures because of the danger of disturbing the alignment of the fragments. It should be remembered that voluntary exercises are to be preferred to faradic stimulation of the muscles.

Summary of Data on the Faradic Current

As with other low voltage therapeutic currents the faradic current has a small but definite field of usefulness. The current is derived from a fairly simple apparatus and is easy to apply. It is indispensable for use in performance of the test for reaction of degeneration and is valuable for stimulating weak and atrophied muscles.

The Interrupted Galvanic and Sinusoidal Currents

The interrupted or waved currents of this group are of low voltage and amperage. The group includes the interrupted galvanic current, the slow sinusoidal current and the rapid sinusoidal current. There are numerous modifications of these basic forms of current for which a uniform nomenclature has not been determined.

The interrupted galvanic current is a unidirectional current which is made and broken, turned on and off, sharply. When passed through normal muscles it will produce quick brief muscular contractions at each make and break of the current. The slow sinusoidal current is an alternating current the volume of which can be represented as traveling in the course of a sinusoid. In other words a graph of the current volume looks like a series of symmetrical waves. The potential rises slowly from zero to maximum, then gradually returns to zero; it then reverses and repeats this action. The rate of alternation usually is 5 to 30 per minute. Smooth muscles and skeletal muscles which are in a state of flaccid paralysis usually will respond to this current.

The rapid sinusoidal current is similar to the slow sinusoidal current with the exception that its rate of oscillation is much greater, the rate being 120 alternations, 60 cycles, or more per second. The rapid sinusoidal current alternates so rapidly that, although it will cause smooth

tetanization of normal skeletal muscles no single stimulus is long enough to produce a contraction in a paralyzed muscle

Modifications of these basic interrupted or waved currents include various types of surging such as the types known as the surging sinusoidal current and the surging sinusoidal current with a sustained peak

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Usually with the rapid sinusoidal current the duration of the period of flow before reversal will be from 1/50 (0 02) to 1/200 (0 005) of a second With the current of 60 cycles the duration would be 1/120 (0 008) of a second because there are 120 alternations to 60 cycles

Action and Uses of the Interrupted Galvanic and Sinusoidal Currents

When these interrupted or waved currents are passed through human tissues, the electrochemical changes, which are produced may stimulate nerves or cause muscles to contract The action has been attributed to concentration of hydrogen or hydroxyl ions

The contractions caused by the interrupted galvanic current are separate and brief hence they do not resemble normal muscular contractions Voluntary muscular contractions are more prolonged and result from a series of nerve stimuli which are said to occur at the rate of more than twenty per second Therefore the interrupted galvanic current is not the most suitable current for therapeutic use and it is employed only for stimulation of weak paralyzed muscles which will not respond to the waved currents There has been a great deal of controversy concerning the rôle of electrical stimulation in treatment for various types of lesions of the lower motor neurons with resultant paralysis Some physicians[17, 18] contend that electrical stimulation will maintain contractility irritability tone and nutrition until such time as regeneration of the nerve takes place if it takes place at all Others[19, 20] are equally positive that electrical stimulation has no place whatever in the treatment of paralysis and may do much harm

Because of this controversy the comparatively recent studies of Fischer[1] are significant He noted that in spite of this prolonged clinical dispute concerning the value of electrotherapy in treating paralyzed muscles almost no experimental data could be found to support the contention of either group He performed tests on laboratory animals with either a tetanizing faradic current from an induction coil or an interrupted galvanic current from dry cells After extensive study and experimentation he reached a number of interesting conclusions Among these were the following If a denervated muscle has been left untreated for about two weeks or more faradic stimulation no longer produces an appreciable contraction In such instances galvanic stimulation will provoke contractions and repeated daily treatments will delay the lengthening of chronaxia to some extent but not nearly so markedly as will early treatment by faradic current The fact that electrical treatment of muscles decreases the rate previously increased by denervation

at which weight and water content are lost and also increases the quantitatively raised but qualitatively impaired metabolism' seems to afford a clue for the explanation of the beneficial effect of the treatment This effect is identical with the training effect on normal muscle produced by electrical stimulation In normal muscles also the weight increases and the metabolism is raised and increased in efficiency by strong electrical stimulation A treated muscle five weeks after denervation has about the same weight as an untreated muscle about one week after denervation The power of a muscle treated for five weeks is appreciably greater than that of its untreated partner It is noted especially that the treated muscle is less fatigable Despite remarkable retardation of loss of weight and diminished loss of dry substance the treatment has failed to improve the contractile mechanism But after reinnervation it seems reasonable to assume that a treated muscle with its higher excitability its greater weight its lower content of water and its increased metabolism could be restored more easily to normal function than an untreated muscle These studies seem significant and would seem definitely to refute the claims of those who say that electrical stimulation plays no part in the treatment of paralyzed muscles

The uses of the interrupted galvanic current in medicine are few It of course is employed routinely in conjunction with the faradic current in performance of the test for reaction of degeneration It is used occasionally also for stimulation of extremely weak paralyzed muscles which will not respond to the slow sinusoidal or to other waved galvanic currents

The slow sinusoidal current is used for stimulation of unstriped muscles and sometimes can be used to produce contractions of paralyzed skeletal muscles The rapid sinusoidal current is employed for stimulation of weak or atrophied muscles which have a normal nerve supply For this purpose it is somewhat less unpleasant than the faradic current

Not only have the interrupted galvanic and slow sinusoidal currents been employed in treatment for lesions of the lower motor neurons but their use has been suggested[1] also for lesions of the upper motor neurons such as hemiplegia or myelitis Electrical stimulation has been employed for prevention of atrophy of the quadriceps or deltoid muscle following injury to the knee or shoulder to improve muscular tone in cardiovascular disorders and to initiate respiration in asphyxia of the newborn

The rapid sinusoidal current can be used interchangeably with the faradic current Therefore the indications listed under Action and Uses of the Faradic Current can be consulted for further information concerning possible uses of the rapid sinusoidal current

Contraindications to the Application of the Interrupted Galvanic and Sinusoidal Currents

Electrical stimulation is contraindicated in cerebrospastic paralysis combined sclerosis of the spinal cord progressive muscular atrophy and myasthenia gravis In stimulation of paralyzed muscles excessive treatment may produce fatigue and do more harm than good Such stimulation always should be applied within limits of fatigue If there is slowing of muscular response which is the first sign of fatigue treatment should be stopped at once

It has been said that if alternating or sinusoidal currents are applied to the cardiac region they may cause cardiac fibrillation It must be stressed once more that electrical stimulation always is less valuable than is voluntary exercise

Summary of Data on the Interrupted Galvanic and Sinusoidal Currents

A few simple modifications of the three basic currents which have been discussed are all that is necessary for satisfactory electrical stimulation of muscles Elaborate apparatus is not required for this purpose The simpler devices are entirely satisfactory for production of muscular contractions There are several uses for such apparatus

DIATHERMY

By far the most valuable form of electrical current for use in medicine and surgery is the high frequency or diathermy current It has been found that if an electrical current is made to oscillate at an extremely rapid rate it can be passed through the tissues of the human body without producing any neuromuscular response hence no electrical shock is produced Under such circumstances both the voltage and the amperage of the current can be increased so that an increase in temperature will develop in the tissues traversed by the current

In this manner a means of producing deep local heating of bodily tissues is obtained without any other effects on these tissues To employ a crude analogy just as the filament of an ordinary electric light bulb glows to white heat owing to the resistance it offers to the flow of a 60 cycle current of relatively high voltage so to a lesser degree will the bodily tissues become heated owing to the resistance which they offer to the flow of this current of relatively high voltage and very high frequency The patient would receive a severe electrical shock from a 60

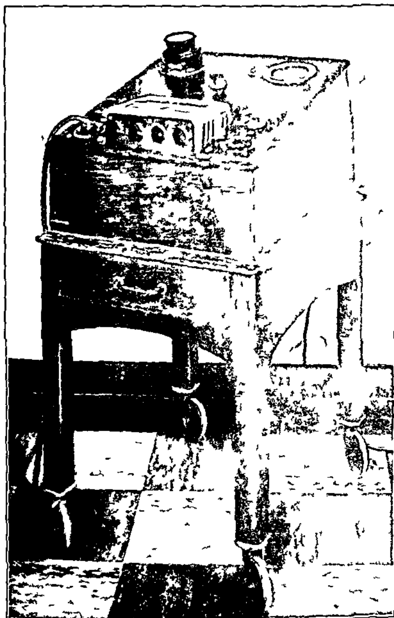


FIG 26 A conventi nal diath rmy machine (From Krusen F H Physical Medi c ne Saunders Ph lad lphia 1941)

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in which the circuits are well described The appliance for the production of short wave diathermy resembles in construction a short wave radio transmitter with the exception that the electrical energy instead of being dispersed from antennas as in broadcasting is confined mostly between

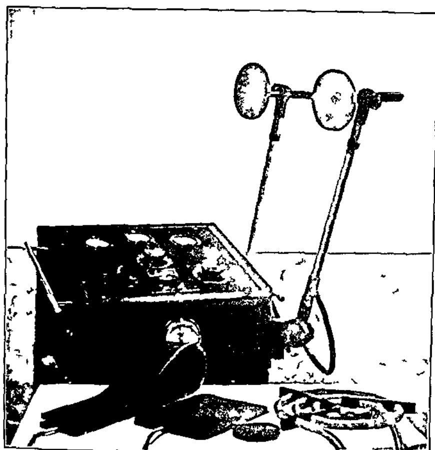


FIG 27 A short wave diathermy machine (From Krusen F H Physical Medicine Saunders Philadelphia 1941)

condenser plates to produce an electrical field or is confined within a coil to produce an electromagnetic field

Human tissues acting partly as conductors and partly as dielectrics when placed within these fields presumably are heated by the production of ionic oscillations and molecular friction Power losses occur and heating of the deep tissues is produced

cycle current of sufficient voltage and amperage to heat the tissues but he receives no such shock from the current of high frequency

Because of the heating of the tissues which are traversed by the current the procedure has been called diathermy This designation has become well established as the proper term for the description of the application of high frequency currents of relatively long wavelengths 500 000 to 3 000 000 cycles per second

Following the development of the triode principle of electronic oscillations radio engineers were able to construct excellent vacuum tube oscillators which would produce currents of much higher frequencies and shorter wavelengths than previously had been employed The newer machines which employed vacuum tubes were able to produce an oscillating current of extremely high frequency from 10 000 000 cycles per second and a 30 meter wavelength to 100 000 000 cycles per second and a 3 meter wavelength

With the development of these new machines it has become the custom in the United States to call longer wavelength machines conventional diathermy apparatus and the new shorter wavelength devices ' short wave diathermy machines In Europe the much less explicit and less descriptive designation "short wave therapy still is employed frequently

Methods of Applying Diathermy

A typical apparatus for producing conventional diathermy consists of (1) a source of alternating 60 cycle current (2) a switch (3) a choke coil current intensity regulator (4) a step up transformer (5) spark gaps (6) condensers (7) a solenoid and (8) an inductor (Fig 26) Such an arrangement delivers a moderately high frequency current to a patient Wires leading from the machine to metal plates on the surface of the patient s body will provide a conductive type of high frequency current for passage through the body With the development of the newer short wave diathermy machine the older conventional diathermy apparatus largely has been discarded Nevertheless it still is useful and sometimes can be employed to better advantage than the newer machine for localizing heat in a small region

The most common type of apparatus for production of short wave diathermy current consists of a simple two tube push pull circuit (Fig 27) The circuit consists of three essential parts (1) the power supply (2) the oscillating circuit and (3) the output circuit For further details the reader can consult an article by Hemingway and Stenstrom

is a thermal one and that within the range between 3 and 30 meters one wavelength has no particular advantage over another

Action and Uses of Diathermy

It has been demonstrated that appreciable rises in temperature of more than 5° F or of 2.75° C can be obtained at a depth in comparatively avascular tissues If the tissues are highly vascular little increase in temperature not more than 0.9° F or 0.5° C will be found It frequently has been claimed by enthusiasts that short wave diathermy will produce certain physiological effects other than those attributable to heating but a large amount of experimental data now has been amassed which seems definitely to indicate that no specific physiological effects other than those attributable to heating exist

The numerous scientific investigations of the effect of diathermy on bacteria now permit the conclusion that neither in vitro nor in vivo are there specific bactericidal effects other than those attributable to heat

Whereas high frequency currents may be employed to great advantage for electrosurgery fulguration desiccation coagulation and electric cutting such applications are outside the realm of this chapter The surgeon who desires additional information on this subject should refer to other sources[23, 24, 25] for details concerning their employment Short wave diathermy currents are not suitable for fulguration desiccation or coagulation but are excellent for purposes of cutting A conventional diathermy spark gap apparatus should be employed for fulguration desiccation or coagulation

For medical purposes that is to heat the bodily tissues within physiological limits short wave diathermy is most effective For such local heating of tissues there are three general types of electrodes condenser plates or pads may be placed on each side of the part to be treated cuffs may encircle an extremity above and below the region to be treated or an induction coil may be wrapped around an extremity or formed in the shape of a flat pancake and placed over a certain region The electrodes always should be spaced away from the bodily surface for a distance of about 2 inches (5 cm) by means of felt pads or folded turkish towels The apparatus then is adjusted to provide comfortable warmth in the region which is exposed to the current

Despite frequent claims that short exposures of not more than ten minutes are sufficient to produce proper heating of the tissues repeated studies in my own department[6] have indicated that it requires at least thirty minutes of exposure to short wave diathermy to obtain an optimal

Physical Principles Concerned in the Application of Diathermy

With regard to the position of electrodes with conventional diathermy it is necessary to have the electrodes in direct contact with the skin or the mucous membranes. This may be unsatisfactory, especially if a large electrode is to be used over an irregular surface. However, if short wave diathermy is to be employed, an insulating pad or layer of air can be interposed between the electrode and the surface of the body. Thus by applying short wave diathermy electrodes at a distance from the surface, it is possible to heat a deeper region of the body without undue heating of the skin.

Selective Heating. — It has been claimed that the newer short wave diathermy currents will produce "selective heating" of various bodily tissues, that is, because different tissues have different dielectric constants they will be heated to a greater or lesser degree. Basing their claims on this therapeutic conception, a number of enthusiasts have concluded that it would be possible, therefore, to heat one organ of the body to a greater degree than another. Although it is true that short wave diathermy will produce selective heating of inorganic substances and of dead tissues, it now has been demonstrated repeatedly that in the living animal, owing to dissipation of heat by the circulation, no such selective heating of tissues can be expected.

Thermopenetration. — For various physical reasons it is evident that short wave diathermy should produce more uniform and deeper penetration of heat than does conventional diathermy. As yet, despite a number of investigations of the problem, there is no conclusive proof of this. Further observations eventually may indicate the comparative thermopenetration of these two forms of diathermy.

Dosage. — At present there is no means for accurate determination of the dosage of short wave diathermy. Watt meters are being developed which may help to give some indication of proper dosage; however, these are not entirely accurate. At present the physician who applies short wave diathermy must rely on his careful observation of the sensation of heat felt by the patient and from this must govern the dosage as accurately as possible. Because of this need for careful observation of the sensations of the patient by a skilled physician or technician, no patient ever should be permitted to control the dials of the apparatus himself.

Wave-length. — It has been claimed by various investigators that different wavelengths produce different effects on the bodily tissues; however, as more and more experimental evidence is amassed, it becomes evident that the only effect of short wave diathermy on the bodily tissue

thermy has been recommended may be mentioned sinusitis Although after adequate drainage has been established local applications of heat may be of slight value in the presence of inflammation of the accessory nasal sinuses the procedure is merely palliative and there is no conclusive evidence that the procedure as often has been claimed ever is a specific in this condition Diathermy has been recommended also as an adjunct in the management of various pulmonary lesions such as bronchitis bronchial asthma and both bronchial and lobar pneumonia In such conditions it must be considered simply as another means of applying heat and it should be employed only as an auxiliary measure in conjunction with other forms of treatment

Contraindications to the Employment of Diathermy

Diathermy should not be employed in the treatment of any condition in which there is danger of hemorrhage Because of the danger of burns the application of diathermy is contraindicated also over regions in which sensation is impaired It should not be administered to the abdomen lower portion of the back or pelvis during pregnancy or during the menstrual period Also it should not be applied over regions in which there may be a malignant growth or tuberculous lesion Some authors believe that diathermy should not be applied in the presence of phlebitis because of the danger of embolism

Summary of Data on Diathermy

It is wise to employ only such diathermy apparatus as has been accepted by the Council on Physical Therapy of the American Medical Association The various diathermy machines which have been considered acceptable information about their degree of efficiency and the approved technics for their use are listed in a booklet entitled Apparatus Accepted by the Council on Physical Therapy of the American Medical Association [1] Every effort should be made to avoid the use of diathermy except when it definitely is indicated Certainly there are enough rational indications for its employment to warrant its frequent use It should not be forgotten however that simpler methods of applying heat may be equally effective for the treatment of superficial lesions Short wave diathermy finds its greatest usefulness for treatment of deeper lesions It unquestionably is the most valuable form of electrotherapy available today When employed in a rational manner it may be used for a multitude of purposes both in medicine and in surgery

increase in temperature and the usual exposure time should be thirty to forty five minutes For further details concerning the technic of application of short wave diathermy other more complete publications should be consulted[16, 7]

Short wave diathermy has been recommended especially in the treatment of suppurative processes diseases of the bones and joints such as sprains dislocations arthritis osteomyelitis and periostitis There still is considerable argument concerning the usefulness of short wave diathermy in the management of fractures Some investigators have expressed the belief that hyperemia caused by diathermy produces demineralization of bones whereas others have felt that the increased circulation accelerates the formation of new bone

Some have stated that the heat produced by diathermy is valuable in the treatment of fractures because of its favorable influence on the associated injuries to soft tissue When so employed it often should be administered in conjunction with massage and exercise Diathermy also has been recommended in the treatment of various types of endarteritis to promote circulation However in such cases there is always danger of producing burns and subsequent gangrene if too intense diathermy is applied directly to the involved extremity Its employment has been recommended also in treatment for varicose ulcers

In the field of cutaneous diseases continental workers have recommended particularly that diathermy be applied for furuncles carbuncles cellulitis and paronychia To date there is no conclusive evidence that diathermy is more effective in such localized infections than are other forms of mild local heating For certain gastrointestinal diseases such as diverticulitis acute enteritis and spastic colitis diathermy has seemed to be of value as a palliative measure A number of good investigators have stressed the value of local applications of intrapelvic diathermy in the treatment of chronic inflammation in the pelvic region as well as for nonspecific prostatitis epididymitis and cystitis Among the diseases of muscles tendons and bursae for which diathermy has been recommended may be mentioned contusions muscular strains myositis fibrositis tenosynovitis and bursitis Among the diseases of the nervous system in which local heating by diathermy sometimes is useful may be mentioned neuritis particularly ischemic neuritis and such conditions as brachial neuritis intercostal neuritis sciatica and trifacial neuralgia Short wave diathermy has been recommended to promote healing and to allay pain in otitis media and in the treatment of furunculosis of the external auditory canal

Among diseases of the respiratory system for which short wave dia

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Effleurage or Stroking — Stroking is the most common form of massage The hand is moved slowly gently and rhythmically in long stroking movements Light superficial stroking produces reflex effects and deep stroking will produce actual mechanical emptying of the veins and lymphatic vessels

Petrissage or Kneading — Kneading is a wringing or compression movement in which the muscles are picked up and rolled squeezed or wrung

Friction — Friction is not as the name might suggest a rapid rubbing of the technician s hand over the skin to produce a frictional effect On the contrary it is a circular rolling movement in which the patient s skin is moved over the subcutaneous structures in small circles The fingers of the masseur remain at one point on the patient s skin and move it around This type of massage tends to loosen superficial scars and adhesions Friction usually is preceded and followed by stroking

Tapotement or Percussion — There are various types of percussion If the surface of the patient s body is struck lightly and alternately first with the ulnar surface of one hand and then with the ulnar surface of the other hand the procedure is called hacking If the part is struck lightly and rapidly with alternate slightly cupped palms of the hands the procedure is called cupping If the tips of the fingers are employed for percussion the method is spoken of as tapping When the flattened palms are employed for percussion the procedure is termed slapping Finally if the relaxed half clenched fists are used for percussion the designation beating is employed Percussion movements will produce stimulating effects and induce peripheral hyperemia

Vibration — Vibration is a continuous trembling movement which is applied to the surface of the patient s body through the tips of the technician s fingers or through his whole hand The vibratory movement is initiated by the muscles of the technician s shoulder and forearm It is an extremely difficult movement and soon tires the masseur For this reason in the few instances in which vibration is required a mechanical device may be attached to the back of the technician s hand to produce the vibratory movement

In most instances the numerous mechanical devices which have been marketed in profusion for pushing pulling twisting turning and otherwise manipulating the human contours are utterly useless For example about ten years ago the public was swept with a wave of enthusiasm for machines which allegedly supplied massage and exercise by means of a strong vibrator attached to a wide belt These so called health exercisers were much in vogue for a short time but because they were like most

MASSAGE

"Massage" is a term used to describe a group of systematic and scientific manipulations of the tissues of the body which are performed best with the hands for the purpose of affecting the general circulation and the nervous and muscular systems.

A better understanding by physicians of the subject of massage undoubtedly would lead to its more extensive use and to methods of application which would be more suitable for the individual patient. Too frequently the physician requests a technician to give a patient some massage without specifying the type, duration or other details concerning the method of massage to be followed. Although on the European continent it frequently is the custom for the physician himself to apply massage, among American and British physicians it usually is customary to delegate this work to technicians. Because of the fact that in the United States there are skillful registered physical therapy technicians and in Britain well trained members of the Chartered Society of Massage and Medical Gymnastics who are well instructed in anatomy and kinesiology, the custom usually is acceptable. Nevertheless even the most skillful technician is untrained in diagnosis and has only a limited knowledge of morbid physiology and pathology, so that the physician always should assume direct supervision of the massage, even though the technician does the actual work.

Mennell[1] said pertinently: "When a medical man orders massage he should not try to hand over his responsibility to the masseur. He should consider the prescription of massage treatment in the same light as he would consider that of a potent drug and watch its effects no less closely, varying the dose and the nature of the dose from time to time according to indications."

METHODS OF APPLYING MASSAGE

The massage movements in the order of their importance are as follows: (1) effleurage (stroking), (2) petrissage (kneading), (3) friction (a circular rolling movement), (4) tapotement (percussion) and (5) vibration (a tremulous or vibratory movement).

Stroking, kneading and friction are the only movements which are employed routinely for therapeutic purposes. Vibratory and percussion movements usually are applied to the healthy individual and rarely are applied to the sick person.

cessive secretions and to cleanse the openings of sweat and sebaceous glands This procedure is particularly useful at the time of removal of splints or casts following fracture Rosenthal[8] found that massage of the skin could cause an increase of local temperature of 3 6° to 5.4° F (2° to 3° C) He attributed these increases of temperature not only to direct mechanical action but al o to indirect vasomotor effects

The mistaken general impression still exists that massage will remove deposits of fat from local regions of the body Careful clinical investigations do not support this impression In experimental studies of this problem Rosenthal[8] found that vigorous massage of the abdominal wall of animals produced no destructive effect on the adipose tissue Following the heavy massage histological sections of the adipose tissue exhibited no destruction of the fat although the pressure of the massage had been sufficiently heavy to produce multiple hemorrhages

It is believed[1] that massage of muscles may improve the supply of blood and tend to remove the excess of lactic acid which develops following exercise Massage can be employed as a mechanical means of stretching or breaking adhesions of intramuscular connective tissue Although it often is thought that massage of muscles may increase their strength this is not the case Muscular strength can be improved only by active exercise

Centripetal stroking will improve circulation by aiding mechanically the return of venous blood and lymph toward the heart It may produce *also reflex contraction of the unstriped muscles of the walls of the vessel* thus assisting in the maintenance or restoration of the tone of these muscular fibers The lightest stroking will empty the superficial veins and lymphatic vessels of an extremity and the pressure in the deeper veins rarely exceeds that of 5 or 10 mm of mercury In order to obtain mechanical assistance to circulation in the deeper vessels the muscle must be well relaxed

Best and Taylor[7] pointed out that light stroking causes the white reaction which attains its maximal intensity in thirty to sixty seconds and then gradually fades in about three to five minutes They concluded that this reaction did not have a nervous basis but was due to direct stimulation of the walls of the capillaries They thought that heavy stroking would produce more enduring dilatation

Massage often is valuable as an adjunct to elevation in the relief of edema of an extremity Massage will assist gravity and also aid in restoring vasomotor tone

Observations[3] through a permanent window of the capillary circulation of the ear of a rabbit have revealed that following massage there is an

such devices almost useless as a means of applying either massage or exercise they soon fell into disrepute

In 1930 Pemberton Coulter and Mock commented concerning these health exercisers as follows 'Doctor Gustaf Zander of Stockholm about 1857 was the first to use mechanical means for massage and exercise His machines will do anything that any of the highly advertised mechanical vibrators will do These machines were given a trial in this country and several large hospitals completely equipped Zander rooms These forms of apparatus have fallen into disuse as will the present widely advertised mechanical exercisers The prediction of these physicians was correct the health exerciser no longer is heard of and such has been the case with all similar mechanical massaging devices

Physical Principles Concerned in the Application of Massage

Massage is an entirely mechanical procedure Usually the hands of a skilled masseur or masseuse serve as the therapeutic agents Mechanical apparatus of various types has not proved suitable for massage because the movements are too complex to be produced satisfactorily by a machine

Mennell[1] said that only two possible effects were obtainable from massage a mechanical effect and a reflex effect It generally is believed that *superficial stroking will produce reflex diminution of muscular spasm* Physicians usually are more familiar with reflexes such as the cremasteric or the plantar reflexes which are produced by irritation of the skin and cause muscular contraction and often they have not realized that the soothing effect of light stroking of the skin may produce reflex muscular relaxation It is easy to demonstrate such reflex muscular relaxation by applying superficial rhythmic stroking in the presence of a recent fracture with associated muscular spasm The gentle stroking often produces sufficient relaxation to permit easier reduction of the fracture

Action and Uses of Massage

Pemberton[3] said aptly There is probably no other measure of equal known value in the entire armamentarium of medicine which is so inadequately understood and utilized by the profession as a whole ' Mennell[1] Coulter[5] and Pemberton[3] all have made definite contributions to our modern knowledge of the action of massage Massage can be employed for its direct action on the surface of the skin to remove detritus and ex

the intramuscular or the periarticular type All these authors[10 11 12 13] agreed that in conjunction with fibrositis fibrous nodules will be found which can be massaged away

Despite the fact that this condition commonly is unrecognized in the United States it seems safe to conclude that the numerous English observers are correct in their conclusions They contended that there is a form of muscular rheumatism commonly called fibrositis which is characterized by the formation of fibrous nodules bands or indurated regions which are acutely tender at first and are associated with muscular spasm and that if the condition becomes chronic the tenderness and muscular spasm tend to disappear

Furthermore English physicians have claimed repeatedly that such indurations can be broken up and made to disappear by means of a special type of heavy stroking and kneading which should be applied directly to the indurations The heavy massage if continued for a sufficiently long period tends to relieve pain tenderness and muscular spasm Apparently fibrositis frequently is overlooked and the value of heavy massage in treatment often has been unrecognized The procedure is palliative rather than curative and recurrences are frequent so that often it will be necessary to employ other methods of treatment in conjunction with renewed applications of firm massage

Diseases of the Muscles — In muscular spasm of the occupational type such as writer s cramp a small localized region of tenderness often is present Friction and deep stroking frequently relieve such tenderness Continued deep stroking and kneading may prove to be a valuable adjunct in treatment

Brisk general massage in conjunction with stroking and kneading of the affected regions has been employed in treatment for pseudohypertrophic muscular dystrophy The massage usually is administered in conjunction with the passive exercise of joints to prevent contractures These procedures of course are merely palliative

For muscular contusions gentle stroking and later kneading may be valuable in relieving pain and stiffness and in promoting absorption of exudate The massage should not be begun until forty eight hours after the injury was sustained

Obesity — It has been mentioned that massage is incapable of removing local deposits of adipose tissue but general massage employed in conjunction with exercise and reduction of caloric intake may be of slight usefulness in the management of obesity The massage sometimes can be employed as an adjunct in the early treatment of weak obese individuals later it can be replaced by carefully graduated mild exercises

increase in the rate of flow of blood and a change in the walls of the capillaries which is evidenced by sticking and emigration of leukocytes It was concluded that the massage produced an increased interchange of substances between the blood stream and tissue cells with an altered and presumably improved metabolism of tissues

For necessarily inactive patients and especially for patients with cardiac decompensation massage can be employed to compensate for the lack of contraction of the muscles of locomotion which normally contributes to the return of venous blood to the heart I agree with Pemberton[3] that this form of massage is not utilized clinically to the extent that it should be

It is said that the influence of massage in increasing the amount of hemoglobin and the number of erythrocytes of the circulating blood ' is beyond question Massage does not increase the lactic acid content of *the blood and the change in the hydrogen ion concentration is not* comparable to that observed following exercise Massage produces no change in the percentage of oxygen saturation but it does cause a slight rise in the oxygen capacity of the blood

If massage is applied skillfully it can be employed to produce either a sedative or a stimulating effect on the central nervous system Massage does not have any immediate effect or great influence on general metabolism There is no immediate or delayed effect on the basal consumption of oxygen the pulse rate or blood pressure of normal persons

Arthritis — *Massage is of considerable value in preventing or* delaying the muscular atrophy which often is associated with arthritis Properly applied it can be employed also in arthritis to improve local metabolism increase circulation and lessen edema In most cases of arthritis massage is preceded by applications of heat and followed by exercise For atrophic arthritis massage alone is useless Usually massage is applied to the muscles above and below the joint rather than directly to the arthritic joint In the management of atrophic arthritis general massage often can be employed advantageously in conjunction with local massage *In hypertrophic arthritis especial care must be exercised to* avoid heavy massage over or too close to the articular structures Massage never should add to the trauma which already has been inflicted on such joints

A leading specialist[8] on arthritis said that few if any advanced cases of arthritis of either the atrophic or the hypertrophic type can be expected to recover without recourse to the principles of physical therapy intelligently ordered rest and massage in particular

Fibrositis — Many English writers have urged the employment of a special type of extremely firm massage in treatment for fibrositis of either

Obstetrical Conditions — Massage frequently is valuable during and following the puerperium Certain conditions which contribute to the discomforts of pregnancy can be benefited distinctly by correct application of massage These include nervous headaches cramps of the legs backache resulting from muscular strain and mild edema of the legs resulting from simple venous obstruction During labor massage of the uterus often is employed by the obstetrician Following delivery massage of the fundus of the uterus is practiced in order to hasten involution On the third day after delivery massage of the legs can be started

Contraindications to the Application of Massage

Massage should not be employed in the presence of malignant growths acute inflammatory processes certain cutaneous affections such as eczema and acne tuberculous lesions acute systemic diseases which are accompanied by fever acute phlebitis thrombosis or lymphangitis Other conditions which contraindicate the employment of massage are undrained osteomyelitis gastric or duodenal ulcer hernia debilitating diseases advanced arteriosclerosis abscesses aneurysm advanced nephritis and acute communicable diseases Heavy massage should not be applied to the abdomen during the later months of pregnancy

Summary of Data on Massage

There is a distinct need for a better understanding on the part of physicians of the action and uses of massage Its limitations also should be known Massage can be employed satisfactorily only if each step in its application is directed properly by a physician who is familiar with its effects and who knows how to modify them to suit the indications The numerous contraindications to the use of massage always should be kept in mind

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Circulatory Diseases — When there is cardiac decompensation skillful massage may aid in restoring compensation by improving the peripheral circulation Curiously enough although massage has an obvious field of usefulness in improving circulation and although it frequently is employed for this purpose on the European continent it rarely is put to this use by American physicians *Every clinician determines the presence of* edema by making pressure with a finger to displace fluids It is obvious that massage could perform the same function on a larger scale and free an extremity of some of the edema This fact however seems to have escaped large recognition in this country[4]

Furthermore in cases of circulatory failure when the patient must remain at absolute rest massage can be employed as a substitute for the normal muscular contractions which usually assist circulation Moderately deep stroking sometimes can be employed in conjunction with other therapeutic measures in treatment of peripheral vascular diseases

Neurological Diseases — Massage sometimes is employed to combat the fatigue depression and irritability often associated with neurasthenia Massage sometimes can be employed to advantage in the management of hysteria but the technician must be familiar with psychotherapeutic methods and must employ massage only as it may be needed For most neuroses massage should not be used indiscriminately Coulter[5] has said that in most cases of traumatic neurosis more symptoms have been rubbed in with massage than have been rubbed out

Massage has been employed as a palliative measure in the management of such neurological conditions as Parkinson s syndrome syringomyelia and Sydenham s chorea Light sedative massage occasionally is used in treatment of peripheral neuritis In certain forms of paralysis such as crutch paralysis and Bell s palsy massage can be very useful in maintaining tone and nutrition of the muscles until volitional control returns

Orthopedic Conditions — Massage has been employed for sprains strains dislocations and fractures to promote circulation relieve muscular spasm overcome adhesions and restore function It is valuable also in conjunction with exercise in the management of postural backache sacroiliac or lumbosacral strain and coccygodynia In the latter condition both external and internal massage are employed occasionally In some instances coccygodynia seems to be due to spasm of the piriformis coccygeus and levator ani muscles and such spasm sometimes can be relieved by internal massage through the rectum

Following amputation massage often is useful in the preparation of the stump to receive the prosthesis

CORRECTIVE OR THERAPEUTIC EXERCISE

The methods of exercise employed in modern therapy have sprung from three systems of exercise (1) the Swedish system introduced by Ling and Spiess (2) the Turnverein system founded in Germany by Jahn and (3) the Delsarte system developed by the French

The modern American technician as a rule does not follow any one of these systems but has adopted that which is best from all of them and has introduced much in addition The Swedish system for some reason has caught the popular fancy in this country and many physicians as well as laymen have the erroneous fancy that anyone who is a native of Sweden is endowed with great skill in massage and gymnastics As a matter of fact the American physician who is familiar with modern corrective exercise immediately becomes suspicious of the individual who claims to be an expert in Swedish exercises because he knows that the modern American technician should be familiar with the best methods of exercise derived from all the ancient systems and should not confine himself to one system only

Today the old systems and the Zander equipment no longer are employed in the hospitals Corrective or therapeutic exercises now are administered usually as free exercises without the aid of apparatus by skilled technicians who are well trained in anatomy and kinesiology Working under direct medical supervision such technicians are capable of providing an infinite variety of corrective exercises which can be modified from day to day to fit the needs of the individual patient

The scope of therapeutic exercise is much broader than most physicians realize It is apparent that every physician should be familiar with the various forms of corrective exercise and that the supervision of the therapeutic exercises should be entirely in his hands As is the case with regard to massage or for that matter any form of treatment the responsibility should not be delegated to a layman

Corrective or therapeutic exercise can be defined as the scientific application of bodily movement designed specifically to maintain or to restore normal function to diseased or injured tissues Exercise can be employed to rehabilitate patients suffering from a wide variety of diseases

METHODS OF APPLYING THERAPEUTIC EXERCISE

Exercises can be performed either actively or passively In passive exercise the motion of a segment of the body is imparted by some out

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ducing motion These muscles act on the three orders of levers commonly encountered in the skeletal mechanism

With a lever of the first order the joint which serves as the fulcrum lies between the weight and the insertion of the muscle which serves as the power With a lever of the second order the weight lies between the point of application of power and the joint With a lever of the third order the type most commonly found in the human body the power is applied at a point between the weight and the fulcrum

The great importance of the normal functioning of these mechanisms in preserving health is stressed by Mackenzie[1] who thought that in most instances health depended on a correlation of all the bodily systems to the erect posture and all health depended on a failure of one or more systems to correlate to it

No matter which order of lever is encountered in the human body practically all of them are arranged so that the distance between the fulcrum and the point of application of power is short For this reason even a slight pathological muscular contracture may cause a relatively marked angulation of a joint Also with this type of lever a muscle must be strong in order to mobilize the joint

Action and Uses of Therapeutic Exercise

Whereas an ordinary locomotive may be only 4 per cent efficient the human body is much more efficient it varies in efficiency from about 20 to 40 per cent[2] When a muscle is subjected to stress it will respond by increase in tension This is known as the stretch reflex A muscle which is held in a shortened position tends to become tonically shortened one which is kept in an elongated position tends to become permanently stretched

Passive movements at first produce little change in the rate of the pulse but as the part becomes fatigued there may be a slow rise in the rate of the pulse On voluntary contraction of muscles the rate of the pulse increases more rapidly The extent of the increase in cardiac rate depends to a great extent on the physical condition of the subject Although the pulse rate of an untrained individual may increase 25 to 40 beats per minute from moderate volitional exercise this can be considered a normal response to moderate exercise The trained athlete's cardiac rate will increase very little because his heart responds to increased effort by increase in the stroke volume of the heart rather than by increase in the rate of contraction It has not been proved however that this increase in the stroke volume is any easier on the heart itself than is an increase in rate

side force The outside force usually is derived from the hands of the technician but can be obtained also from voluntary effort of another segment of the patient's own body or from a machine Active exercise is accomplished by volitional movement by the patient of the involved segment or segments of the body

Therapeutic exercise is classified best under four headings (1) passive exercise or relaxed movement (2) active assistive exercise in which the patient makes a voluntary movement and is assisted in making it by the technician or by some other force (3) active or free exercise and (4) active resistive exercise in which the patient makes a voluntary effort to move the part and is resisted in such movement by the technician by some other outside force or by his own physiologically antagonistic muscles

Passive exercise may vary from the gentlest of slow rhythmic movements such as are employed in the early stages of post fracture mobilization to the extremely forceful movements sometimes used to overcome fibrous ankylosis of joints which are so rigorous that they must be administered only when the patient is anesthetized Practically all forms of manipulative surgical procedures can be classified under the heading of passive exercise Between the two extremes of passive exercise lie various gradations of passive movement which must be understood thoroughly by the technician

Although *active exercises* usually result in movement of joints there is one form which frequently is employed for therapeutic purposes in which movement of the joints does not occur This form of active exercise is called *static exercise* or *muscle setting* In muscle setting the patient simply contracts and relaxes a muscle or a group of muscles without moving a joint The procedure has been likened to a muscle dance and has the advantage of maintaining circulation and muscular tone and of preventing atrophy without disturbing the position of bones and joints It often is employed to exercise the muscles of an extremity during a period of enforced immobilization

Correct use of *resistive exercise* often is the only way to make one group of muscles work alone and to exclude its antagonists

Physical Principles Concerned in the Application of Therapeutic Exercise

As with any mechanical device in the mechanical acts of the human body movement is obtained by the action of a force on a lever Each of the 434 skeletal muscles is a simple independent force capable of pro

rected especially toward teaching the patient to make a prolonged voluntary expiratory effort and to develop ability in abdominal breathing

Exercises play an extremely important part in the management of the residual effects of poliomyelitis. The physician desiring detailed information concerning such exercises should consult the excellent small and inexpensive booklets on this subject by the Kendalls[1] and by Greteman and Jackson[13] as well as *the free booklet by Stevenson*[14]. *Other* valuable communications on this subject include those of Hansson[1], Legg and Merrill[16] and Lovett[17].

Another group of patients who have been neglected much and who receive great benefit from prolonged training in corrective exercise is the throng of children suffering from cerebral palsy. Because of the limited facilities which are available for proper training of these unfortunate youngsters and it has been estimated that there are 108 treatable cases of cerebral palsy for each 200 000 population, it often becomes necessary for a parent to carry on the training of the child at home. I have found that Girard's excellent monograph[18] is a valuable guide for such parents. Other books to which these parents can refer include the ones by Fischel[19], Rogers and Thomas[0] and Abele and Greteman[1]. In addition every patient with cerebral palsy can get a great deal of inspiration by reading the semibiographical book by Earl R. Carlson[*], himself a sufferer from cerebral palsy, who has devoted his career as a physician to the treatment of the severely birth injured.

Coulter[23] has described a set of modified Frenkel co-ordination exercises which can be employed to advantage in the treatment of combined sclerosis and tabes dorsalis. He has given also an excellent description of the proper methods of employing exercise in cardiac diseases and in the management of hemiplegia. Sever[4] has presented detailed information concerning the employment of corrective exercises for obstetrical paralysis. Elsewhere I[7] have given a description of exercises of individual joints following trauma.

Occupational therapy is a form of therapeutic exercise and anyone interested in this extensive field of therapy should refer to the writings of Davis and Dunton[5], Dunton[6], Mock[7] and Mock and Abbey[8].

To summarize concerning the uses of therapeutic exercise, one may say that general postural exercises are required in the management of such conditions as scoliosis, kyphosis and lordosis. Postural exercises may benefit or may prevent orthostatic albuminuria, postural backache, chronic postural strain, exhaustion states or functional decompensation of the muscles of the back. Foot postural exercises may be useful in treatment of pronation of the feet or in treatment of breaking down of

The cardiac rate of the normal individual should return to normal levels within a half hour following moderate exercise. If the exercise has been exhausting the rate of the pulse may remain accelerated for several hours. Because of these facts it becomes obvious that measurements of the rate of the pulse and the length of time that the pulse remains accelerated are good indexes of the amount of exercise which a patient can tolerate.

Best and Taylor[3] have estimated that the flow of blood through active muscles may be twenty or more times as great as the flow during rest. During exercise a much greater portion of the capillary bed is supplied with blood. Both arterial and venous blood pressures are increased during exercise. The part which active exercise takes in assisting circulation is appreciated insufficiently by many physicians and the deleterious effects of prolonged rest often are overlooked.

Exercise tends to increase general metabolic activity. Even very slight exercises such as writing may increase the metabolic rate 25 to 50 per cent above the basal level. Vigorous exercise may increase the metabolic rate to ten to twenty times the basal level.

It is impossible within the limits of this chapter to describe in detail the exercises which should be employed for various diseases. Therefore when possible I shall refer the reader who wishes detailed exercises to suitable sources of information.

Corrective exercises may be extremely useful in the management of postural deformities. The physician, who is interested in this subject should refer to the report of the Subcommittee on Orthopedics and Body Mechanics of the White House Conference on Child Health and Protection[4] and to the textbooks by Goldthwait and his associates[5] and by Phelps and Kiphuth[6] which deal fully with this important problem. Elsewhere[7] I have described the exercises employed at the Mayo Clinic for treatment of weakness and pronation of the feet as well as exercises for postural backache, lumbar lordosis and scoliosis. Kleinberg[8] has written an excellent monograph on scoliosis.

One of the most interesting recent developments in the field of therapeutic exercise concerns its employment for the control of some of the symptoms of bronchial asthma. The Asthma Research Council of King's College London[9] has published an excellent small booklet which is well illustrated and inexpensive and which can be employed by the patient as an instruction manual while learning the exercises. Livingstone and Gillespie[10] and Bray[11] have reported favorably concerning the efficacy of these exercises in relieving some of the distress of the asthmatic attacks and even in aborting the attacks. These exercises for asthma are di

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the longitudinal or transverse arches of the feet Exercises may be valuable in overcoming muscular, tendinous or fascial contractures

Among the medical conditions, which often can be benefited by exercises of certain types can be mentioned asthma arthritis cardiac disease cerebral palsy combined sclerosis hemiplegia poliomyelitis and tabes dorsalis Among the surgical lesions which can be helped by various types of exercise can be mentioned contusions sprains strains dislocations fractures amputations peripheral nerve lesions and obstetrical paralysis Exercises of the legs may prevent postoperative thrombosis and abdominal exercises can be employed to strengthen the muscles following pregnancy or prior to herniorrhaphy

Contraindications to the Employment of Therapeutic Exercise

There are few contraindications to the use of exercise because activity is a normal state In some instances however exercises are overdone or are performed incorrectly Following injury to certain joints particularly the elbow if exercise is started too early or if passive movement is applied too vigorously further trauma and eventually ankylosis may result

Patients who have neurocirculatory asthenia or effort syndrome tolerate exercise poorly In the presence of cardiac disease exercise although not usually contraindicated should be employed only with great caution and after proper testing of the tolerance of the patient to exercise

If employed injudiciously exercise may precipitate hemorrhage loosen emboli or cause similar disastrous results

Summary of Data on Therapeutic Exercise

Corrective or therapeutic exercise now is applied or directed usually by skilled technicians working under direct medical supervision Exercise if at all strenuous should be prescribed only after a careful examination of the cardiovascular system Such exercise is useful in many diseases and is an indispensable part of modern therapy

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CHAPTER XXII

THE PHARMACOLOGICAL BASIS OF MEDICINE

By L. G. ROWNTREE

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Introduction

To the thinking physician treatment does not consist merely in applying measures of relief. The essence of treatment consists in recognizing the pathological process, in understanding its nature, its cause, the mechanism involved in its production and in the development of its clinical manifestations, in knowing the character, extent and probable outcome of the resulting functional and morphological changes, in valuing correctly the significance of clinical and laboratory findings, in ascertaining the indication for, in knowing the mode of action of, and the most effective methods of applying measures for its prevention, abortion, amelioration or cure.

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defenses against disease and is ingenious in meeting difficulties and dangers Vicarious activity and sharing of function is resorted to repeatedly Successively or simultaneously several lines of defense may be called into play and must be overcome before a vital function is actually endangered Where the cause is beyond attack treatment may so affect this balance that despite an irremovable cause and an all but exhausted reserve function is maintained and life goes on without disabling symptoms and perhaps without serious restrictions

The requisites of treatment are (1) correct diagnosis (2) a true conception of the cause and nature of the derangement (3) familiarity with the manner in which the derangement can be corrected and (4) knowledge concerning the means whereby this may be effected

These appear simple matters withal but they are the revelations of succeeding ages—the handiwork of evolving science Now as in the days of Hippocrates Experience is fallacious and judgment difficult

Oliver Wendell Holmes says The debris of broken systems and exploded dogmas form a great mound a Monte Testaccio of the shards and remnants of old vessels which once held human beliefs If you take the trouble to climb on top of it you will widen your horizon and in these days of special knowledge your horizon is not likely to be any too wide We can with profit consider the evolution of medical doctrines underlying the treatment of the past study the methods and beliefs of our forefathers observe their mistakes and successes and the causes of each and compare in these respects the medicine of the past with that of to-day

The Historical Evolution of Medical Doctrines

Primitive man found himself confronted with functional disabilities He suffered not from disease but from symptoms headache jaundice chills blindness or weakness The cause nature or the significance of the symptoms the underlying disease the nature of the derangement prognosis and the treatment were all unknown Doctors textbooks and medicine were not in existence Biology anatomy physics chemistry physiology pathology pharmacology and therapeutics were still undreamed of Education mental training observation logic and experimentation drugs and instruments were all lacking When sick he had recourse merely to his fellowmen to the animal world about him and to himself He could observe listen imitate speculate imagine and obey He already believed in a supernatural being who was responsible for all he could not understand Surrounded by ignorance and superstition he was the recipient of kind hearted well meaning advice or treatment born of actual experience in some instances more often of

A correct diagnosis is the first essential to treatment Direct and specific therapy begins with diagnosis failing which general or palliative measures only are possible It is to be recognized that with or without diagnosis cures result at times the work of nature not of medicine

Doctrines control therapy Treatment is good or bad according to whether doctrines are true or false These are subject to evolution Verified and established they constitute the science of medicine Their relation to treatment is twofold They concern the nature and mechanism *of pathological processes on the one hand and on the other the mode of* action of measures of relief

In treatment there are two fundamentally different points of view of disease viz the morphological and the functional Both are important The former as pathology has dominated the field of medicine The latter pathological physiology is more difficult to acquire but is essential to therapy since generally speaking drugs affect function rather than form Not until the physician sees a deranged function as well as a lesion will he become a master of treatment Recognition of derangement of function presupposes a knowledge of normal function Physiology therefore becomes the basis or starting point of therapy the diagnosis incorporating a physio pathological conception of disease

Pharmacology deals with the action of drugs Though it be youthful it is already a vigorous science It brings with it to the bedside the tools of science *investigation experimentation* standards exactness in measurement observation and analysis It necessitates and hence develops critical judgment It reveals facts concerning changes in bodily function wrought by the action of drugs the mechanism whereby these changes are effected and not infrequently uncovers physiological processes previously unrecognized It yields quantitative results One of the great weaknesses of drug therapy today is the lack of quantitative determination of results Many drugs are threshold bodies that is they must reach certain levels in the body before they exercise beneficial effects On the other hand the majority of them in the event of overdosage lead to untoward effects resulting in the nullifying of therapeutic action to exacerbations of the original symptoms or in the appearance of other untoward clinical manifestations

In practice the end may be attained by various measures acting in different ways In order to obtain maximum results familiarity with the mode of action of the remedy is essential and a treatment must be employed which combats the pathological process as near its source as possible preferably by one which eradicates the cause

Health is the normal balance in physiological functions In the organism factors of safety are large Nature has provided many

Egyptian Medicine

This is revealed through the study of tombs pyramids and ancient writings From the tombs we learn of Sekhet enanch the first physician known to history who lived about 3000 or possibly 3500 B C and of the existence in his day of the lancet and of a cupping instrument But our chief knowledge of Egyptian medicine is derived through the Ebers Papyrus which was written about 1550 B C This is mainly a collection of receipts and from it we learn something of the therapy of early Egypt thus Schepen (probably the poppy) is useful to soothe crying babies Against all kinds of witchcraft a large beetle cut off his head and wings boil him put him in oil and apply to the part Then cook his head and wings put them in serpent s fat warm it let the patient drink it To make the skin of the face smooth soak meal in spring water Let her wash her face daily and then apply the meal To keep away mice smear everything possible with cat s fur Pills potions inunctions inhalations and plasters were all used in these days

It also contains some remarkable passages relating to diagnosis One reference to the circulatory system is particularly interesting The vessels are said to run in pairs and to contain not only blood but air water milk and other fluids In the doctrine of the heart as the center of the vascular system and in the importance attributed to the pulse the Egyptians were in advance of Hippocrate If the physician place his fingers on the head neck hands arms feet or body everywhere he will find the heart (i e the pulse) for the vessels go to all parts *

The Berlin Papyrus which is of somewhat later date contains many prescriptions and abounds in incantations More than the Ebers Papyrus it emphasizes the supernatural origin of disease

Egyptian medicine just as Egypt itself marked time for nearly 3 000 years In fact judging from the relative popularity and success of Egyptian and Greek physicians at the time of Hippocrates and also later the Egyptian physicians appeared to be hopelessly outclassed

Hindu Medicine

Our knowledge of Hindu medicine is revealed through the Vedas or Works of Wisdom The 4th or Atharva Veda written about 700 B C and later supplementary Vedas are the most important from the standpoint of medicine From them we learn of the medical work of

From Withington s (1) Med al Hist ry from the Earliest Times To Withington the author is indebted for most of the historical sketch here presented Garrison (1) and Baass (1) have also been freely consulted

pretense of knowledge assumed for gain or prestige He desired relief from sufferings and restitution to health He followed his instincts or natural inclinations usually adopting the expectant principle of treatment lying at rest awaiting recovery This failing he consulted with his fellowman and adopted his advice or appealed to the supreme being for relief In the event of recovery he sang the praises of the treatment and its author or lifted his voice in thanks to the Almighty

The savage s conception of disease is essentially spiritualistic Supernatural agencies are of various kinds (1) independent devil born demons of disease, (2) departed spirits ghosts or spirits of the dead, (3) spirits of slain animals (4) human enemies who act through their own supernatural powers by casting spells or indirectly through one or other of the types of spirits already mentioned and (5) spirits acting through the direction of the Almighty to aid in the administration of punishment or the wreaking of vengeance on man for his manifold shortcomings and sins The latter group is the most important since in them belief still exists to some extent even among civilized nations and they were responsible to a large extent for the sacerdotal trend of early medicine

According to Withington ([1]) three methods of procedure have been found effective by the savage medicine man in combating supernatural agencies of disease (1) rendering the body an unpleasant abode for the *intruding spirit through squeezing beating starving or* fumigating it or through the use of nauseating drugs which result in vomiting (2) offering the spirit a more pleasant abode for instance the demon of jaundice can be enticed into a yellow canary and that of ague into a cold clammy frog (3) the intervention of other spiritual forces* The first or what may be considered as expulsion by violence is repre*sented by emetics and massage the second or w ly* seduction finds expression in the ' signatures of the middle ages and perhaps in the similia similibus curantur of our day and the third or the intervention of other spiritual forces is largely responsible for the role played by the priesthood in the history of medicine

Our knowledge of the medicine of uncivilized or early civilized man is derived largely through ancient writings or their translations through folklore through the tracing back of peculiar customs and through investigations of recent date of peoples still uncivilized (Madagascar Tahiti Indians of North and South America)

* This idea also resulted in the belief in witchcraft wherein the same power was used for purposes other than good

paired so long as each humor remained in its own place and in its proper proportion relatively but disease resulted from disproportionate amounts and from an element out of its proper sphere In this conception quantities and interdependence of function are obviously recognized In other words Hippocrates conceived organization in the body but his false doctrines of pathology precluded the possibility of a scientific foundation for medicine

Early Greek medicine was not entirely sacerdotal Priests philosophers and physical trainers practiced medicine as well as physicians proper But whereas the physicians practiced the healing art the priest *corresponded to the mental or faith healers philosophers to medical* scientists or physiologists and the physical trainers to bone setters of later centuries The physicians and the philosophers however were responsible for medical progress

Hippocrates the father of medicine born 460 B C flourished in the golden age of Pericles a contemporary of the most brilliant group of men known to history He was a practicing physician and a philosopher By virtue of his dual interest he clearly separated the two His greatest contribution to medicine was his rejection of the supernatural In this he was influenced to some extent by his environment for at that time the Greeks were in a transition period falling away generally from their belief in mythology That his rejection of the supernatural resulted in his other contributions to medicine is within the realm of possibility for what is more natural than that one needing support in his anomalous position as champion of natural causes for disease should undertake to prove the cause nature and course of disease?

In his study of disease he emphasized the necessity of accurate observation describing the facies and the splash bearing his name He made clear concise clinical records more than forty of which are preserved and from which it is possible in some instances to make diagnoses Diseases were considered in their entirety the course and final outcome being noted He recorded his deaths which were relatively numerous He was the first to properly value prognosis stating that though cure was the most important consideration it was well for the physician to be able to predict the outcome of any illness His methods were those of science accurate observation careful records interest sustained to a conclusion in an attempt to predict the outcome from the facts available

Of his treatment little is known except that recognizing the limitation of diagnosis and of therapy he insisted on considering the individual rather than the disease and above all things on doing no harm Treatment to him consisted of assisting nature for his belief was strong in the vis medicatrix naturae environment diet bowels sleep and all

Charaka and Susruta which indicate that the Hindu medicine of 300 B.C. to 750 A.D. (the period of Buddhist predominance) compares favorably with the contemporary Hellenic medicine. The Hindu medicine contributed much to surgery and to organized medical effort such as medical teaching, army sanitation, hospitals and asylums for the blind and lame.

Surgery was favored rather than medicine; thus by Susruta new noses were created from cheek and forehead flaps, supraorbital nerves were sectioned in neuralgia, even laparotomies were suggested. In writing of his calling he says: "Surgery is the first and highest division of the healing art, least liable to fallacy, pure in itself, perpetual in its application, the worthy product of heaven, the source of fame on earth."

Early Greek Medicine

Hippocrates was the founder of Greek medicine and of medicine in general. However, prior to his time medicine had made considerable progress. Homer's account of medicine relates mostly to surgery, but he introduces us to drugs, "pharmakon," which in the "Iliad" refers to remedies externally applied and in the "Odyssey" to either poisons or charms. He also intimates that knowledge of drugs constitutes a criterion for judging the ability of a physician. In his time medicine and surgery were definitely distinguished, the distinction having been made primarily by Æsculapius, for Machaon, one son, was endowed with skilled hands to draw out darts and make incisions, while to Podalirius, the other, was given all cunning to find out things invisible and to cure that which healed not. In Homer's day "incubation" flourished before the altars of the Asclepieia or temples of Æsculapius. The patient after priestly preparation lay down to sleep before the altar, whereupon was revealed to him by dreams or through the priests those things necessary for recovery. In this way many miracles were wrought.

Empedocles, B.C. 490-430, is also worthy of mention because he laid the foundation for the humeral pathology of Hippocrates and introduced the four elements into medical philosophy. Withington (1) presents a fragment of one of his poems, "On Nature":

> Listen first while I sing the fourfold root of creation
> Fire and water and earth and the boundless height of the ether
> For thereupon is begotten what is, what was, and what shall be

Hippocrates adopted this idea of "fire, water, earth and air," but enlarged upon it. He considered heat, cold, dryness and moisture as four corresponding qualities, and blood, phlegm, yellow bile and black bile as the four corresponding bodily juices or humors. Each humor had its own seat; thus for the blood, the heart; for phlegm, the brain; for yellow bile, the liver; and for black bile, the spleen. Health was unim

(b) on Timaeus from the hand of Plato Unfortunately Plato was unsound as a physiologist and medicine built on his physiology lacked *firm foundation and in consequence suffered greatly*

For a thousand years the School of Alexandria flourished In it were made numerous dissections and many important anatomical discoveries It is credited with many vivisections on criminals and captives In anatomy Herophilus and Erasistratus worked side by side having a community of interests in anatomy but differing widely on the question of treatment The former followed Hippocrates the latter while *operating fearlessly rejected bleeding as too depleting and adopted* extremely small dosage in drug therapy On the question of treatment they continued irreconcilable each founding his own school of therapy

The shortcomings of the dogmatists while numerous can be readily overlooked in the light of their high ideal They contributed largely to the science of medicine creating anatomy and establishing as a principle *medicine based on physiology Their weakness lay in their excess* of theory

(2) *The Empiric School* arose in Alexandria splitting off from the dogmatists about 280 B C as the result largely of the extravagant theorizing of the latter The founders were pupils of Herophilus Philinus and Serapion by name They despised anatomy physiology and pathology were uninterested in the cause of disease claiming that the cure and not the cause was the vital question They accordingly adopted symptomatic treatment and with it a correspondingly narrow point of view They sought specifics and increased markedly the number of remedies without improving treatment

One great man they produced namely Heraclides of Tarentum born B C 230 the greatest therapeutist of ancient times He might qualify to day as a *pharmacologist Though an empiricist he did much to* combat the evils of that system He investigated the clinical effect of drugs utilizing only those he had personally studied and he did much to place therapy on a scientific basis His greatest work was entitled On the Preparation and Proving of Drugs in which he points out the virtues of opium which he finds useful in sleeplessness spasm and colic cough cholera and serpent s bites and locally in the form of poultices in *painful ophthalmia He advocated water for fever and* treated brain fever on logical grounds His principles had they been followed would have relegated empiricism to the background and resulted in rational treatment based on experimental therapy

Aristotle the greatest of Greek philosophers was a great exponent of empiricism As the originator of logic he was naturally forced to forsake the *dogmatists with their innumerable untenable theories* In

the natural functions receiving appropriate attention Purgatives and bleeding he used most frequently Treatment was individualistic the patient s comfort feelings and wishes being consulted and considered as far as possible

His aphorisms alone would have sufficed to bring his name down through the ages revealing his philosophical outlook on life and his great store of wisdom Hippocrates not only stands as the father of medicine but as the greatest medical character of all times In founding a school of medicine he took the final step which made his influence permanent The School of Cos embodied his teachings and ideals Through it his medicine and his inspiration were handed on not only to his pupils but to succeeding generations Such was his influence that his teachings held sway almost unchallenged for two thousand years while some of his principles guide us even today

Greek Medicine Subsequent to Hippocrates

The School of Cos became the center of Hippocratic medicine as the School of Cnidus under Euryphon insisted more on accuracy of diagnosis and on vigorous treatment but lacking instruments of precision and correct fundamental conceptions of disease vigorous treatment was applied frequently to the patient s serious detriment and ofttimes with disastrous results

The interest taken in medicine just subsequent to Hippocrates was little short of remarkable The up to date monarch of the day delighted in medical discussion and in medical problems Mithridates at Pontus became the most famous of toxicologists Attalus of Pergamus planted a famous poison garden while the Greek kings of Egypt exhibited unusual interest in all things medical About 300 B C Ptolemy the First established a museum in Alexandria and that city from that time on became the center of medicine and of learning generally a fact well attested by the fame of its library Three great schools of medicine arose subsequent to Hippocrates

(1) *The Dogmatic School* —It advocated rational medicine the cause being the important factor to determine and remove Galen credits Hippocrates with founding this school others Thessalus and Draco supposedly sons of Hippocrates Praxagorus of Cos Diocles the Alexandrine anatomist Herophilus and Erasistratus were its leading spirits They recognized the necessity of basing medicine on physiology Herophilus (student of Praxagorus) and Erasistratus were the actual founders of anatomy physiology still remaining in the embryonic stage Authority in physiology rested in (a) On the Nature of Man a treatise written supposedly by Polybius son in law of Hippocrates and

Celsus the Cicero Medicorum wrote De Re Medicina which outlined perhaps better than any other publication the medicine of his time but Celsus was not merely a doctor He wrote equally well on many subjects He tells us that in his day medicine was divided into three fields dietetics pharmaceutics and chirurgics

Galen 131 200 was also a founder of a system—one that combined much of the best of dogmatism and empiricism and also of methodism although to the latter he was utterly opposed Physiologist and anatomist as well as practicing physician he wrote prolifically on many subject Through him comes to posterity much of our knowledge of Greek medicine

Public opinion in Rome being adverse to anything quite so brutal a the dissection of the human body as an anatomist he dissected various animals thereby laying the foundation for comparative anatomy He recognized the three coats of arteries and demonstrated that the vessel did not contain only air His physiology like that of the dogmatists was marred by much theory Long before the discovery of oxygen he pondered over the question of body heat declaring that when that part of air which supports combustion was identified we would have the secret of life and of body temperature To him belongs the credit of distinguishing motor sensory and mixed nerves for he recognized their true role in the organism

Galen s medicine rested on anatomy and physiology Disease he says is an abnormal affection of the body giving rise to a lesion of function and may affect an individual organ a system or the body as a whole He recognized three kinds of causes exciting predisposing and proximate Symptoms are of three varieties (1) altered function (2) vitiated qualities and (3) results of these two morbid excretion and retention He differentiated signs and symptoms Signs to him might be either diagnostic or prognostic in character

In his therapy he accepted experience with the empiricists but recognized the cause as the first indication in treatment thus upholding the dogmatists in rational therapy But symptoms also served as indications and could be met sometimes by similars and at others by contraries In addition other considerations were important in indications namely temperament season and environment

In the history of medicine Galen alone has vied seriously with Hippocrates To be sure he had the advantage of 500 years of progress For a thousand years his principle and practice though somewhat modified by mysticism and magic held sway through the middle ages For leadership he competed with Hippocrates but untinctured Greek medicine on being ushered into western civilization proved its superiority with the

fact so far as medicine is concerned he devoted himself almost entirely to criticisms of the theories of the dogmatists Constructively he labored with anatomy in which field he rivaled even the founders of the Alexandrine School

The famous tripod the basis of the empirical system of therapeutics supposedly made possible the discovery or creation of specifics for symptoms or syndromes It consisted of (1) observation and experiments (autopsies) (2) contemporary and earlier experience (history) and (3) conclusions based on similar conditions (analogy) At a later date was added epilogism whereby past events could be inferred from present conditions

(3) The third school *Methodic School* arose under Roman influence and is described under that heading which follows immediately

Roman Medicine

The march of time shifts the scene from Greece and Alexandria to Rome but Roman medicine as all medicine until the time of Harvey was Hellenic in reality reflected Greek medicine

Asclepiades was the first great physician of Rome incidentally the most successful practitioner of ancient times and the prototype of the fashionable physician He introduced into medicine a theory important because it subsequently became the foundation of methodism and at a still later date reappeared in the form of Bruonianism According to him the body consists of various sized atoms with intervening channel and pores through which the smaller atoms circulate Disease consists of relative changes in the size of the pores and particularly in the blocking of pores He also believed that alterations in the solids of the body could cause disease as well as humeral changes drew a clear distinction between acute and chronic diseases and was a great advocate of air as a therapeutic agent

The Methodic School—This the last of the great schools of antiquity found its origin in the principles enunciated by Asclepiades Themison despising the dogmatists in their search for specifics for the cure of symptoms founded a simpler system of medicine based on the fact that diseases have symptoms in common Symptoms are the result of the relaxation or contraction of pores for Themison worked on the principle *contraria contrariis* and drugs were found laxatives and astringents to relax the contracted and constrict the relaxed These doctrines were brought to their greatest stage of perfection by Thessalus who introduced alterative treatment and laid great stress on the subject of diet

The medicine of Rome was the medicine of Galen It is true that

first book exclusively devoted to surgery appeared the work of Albucasis Drug therapy flourished as never before The first Pharmacopeia was issued *from the hospital at Gondisapor* Mesue the Younger in 1015 wrote a book on Materia Medica In these publications drugs introduced or popularized by Arabian physicians are duly discussed such as camphor senna cubebs rhubarb cloves musk syrups rose water and alcohol These works served as the basis for the western pharmacopeias and were consulted almost to our own times

During the dark ages medicine degenerated into medieval scholasticism The School of Salerno rose and fell (1000 1200) The thirteenth century appears brilliant mainly because of its somber background Medicine produced but one outstanding figure prior to Basil Valentine and Paracelsus namely Arnold di Villanova 1235 1312 one of the early *members of the faculty of the famous School of Montpellier* Like other great men of early times he also was versatile in fact a doctor in four faculties medicine law theology and philosophy His chief claim to our attention however is by virtue of his interest in alchemy and his search for the universal remedy or the elixir of life Alcohol to his mind constituted the nearest approach With it he made extracts of various plants laying in this way the foundation for our present tinctures

Medicine of the Renaissance

With the revival of learning came the revival of medicine At this time the mystics or astrologers were in the ascendency and the administration of medicine was controlled largely by the signs of the Zodiac Witches were being industriously hunted down Alchemy was beginning to play a role in the life of the people especially since alchemists were devoting their attention to medicinal remedies instead of transmutation of metals In this setting appeared Basil Valentine and Paracelsus

Basil Valentine the Benedictine monk of Erfurt is shrouded in mystery His works were not published until a century after his death and by some are considered to be from the hand of Paracelsus On the contrary others hold that Valentine actually supplied the ideas so loudly acclaimed by and usually accredited to Paracelsus Valentine's labors in alchemy resulted in the recognition of salts of antimony nitrates of mercury zinc bismuth hydrochloric acid sugar of lead and in methods of producing sulphuric acid and ammonia To mercury he ascribes great value but the noblest of drugs is the quintessence of antimony

Paracelsus 1493 1541 justly or unjustly receives the credit of being the founder of medical chemistry He has been called the Luther of Medicine Bombastic conceited abusive and scurrilous in his attacks

result that Hippocrates was adjudged the true father of medicine even as he is today

Influence of Christianity on Medicine

With the advent of Christianity a mixture of religion and medicine was again attempted with the usual result lack of progress which lasted in this instance for a thousand years Christianity influenced medicine in three ways (1) by restoration of primitive theories of disease (2) by restriction of free thought (3) by religious controversies which monopolized the best efforts of thinkers for centuries

Arabian Medicine

In the year 632 wild barbarian tribes from Arabia descended upon the Roman Empire and within a century stripped her of her most valued eastern provinces Imagine the surprise of Europe when the victorious barbarians demanded in the terms of peace the right to collect and purchase Greek manuscripts But the Arabs were not altogether barbarians Wild and vigorous by nature they were nevertheless endowed mentally with great love of learning

The cradle of Arabic medicine was at Gondisapor where the Nestorian School was located and where later there arose one of the most famous hospitals and libraries of medieval times These people were remarkable as translators and compilators and through their efforts much that was good in ancient medicine was translated preserved and handed down to western civilization

Although Arabian medicine is replete with interesting anecdotes no great progress was made The torch of Greek medicine was kept burning in Arabia while elsewhere it was stifled or allowed to go out Two only of the many interesting figures of Arabian medicine will be mentioned Rhazes the Experimentator and Avicenna the Versatile

Rhazes gave the first description of measles and of smallpox He experimented with drugs both on animals and humans found metallic mercury markedly toxic for monkeys and introduced the extensive use of mercurial inunctions His Continens in nine volumes was a storehouse of information for succeeding generations

Avicenna's Canon however surpassed in popularity all other medical writings of Arabian origin In it he attempted and partially succeeded in reviving the teachings of Galen and Aristotle The Canon became the textbook of medicine for the following four centuries

During the five hundred years that Arabia flourished hospitals scientific institutions academies of learning and great libraries sprang into existence at Bagdad Cairo Damascus Cordova and Gondisapor The

theories failing longer to satisfy the profession The Anatomical Exercise on the Motion of the Heart and Blood in Animals 1628 ushers in a new physiology and the science of medicine Admittedly the profession was loathe to accept but Harvey defended his thesis despite the most bitter persecution and in so doing demonstrated once and for all the advantages of the experimental method The discoveries by Pecquet of the thoracic duct by Rudbeck of the lymphatics the ocular proof of the circulation in the lung of the tortoise by Malpighi and the introduction of the microscope by Leeuwenhoek still further established the practice of furnishing experimental proof with any new claim

But probably medicine profited more from without than from within Not alone were needed experiment and demonstration but training in methods of thought This was supplied by Bacon and Descartes the former formulating The Principles of Inductive Science and the latter clearly distinguishing the materialistic from the vitalistic Galileo was creating the sciences of physics and mathematics while Sanatorius through his assistance was applying the thermometer and the scales to physiology *Borelli was utilizing mechanics and physics in investiga*tions of the mechanics of motion In other words science and the instruments of science were coming into general use in medicine as elsewhere Iatro chemistry iatro mathematics and iatro physics were laying the foundation of the new medicine and men were beginning to specialize in various fields of medicine and its underlying sciences

Space does not admit of detailed consideration of its various branches but an attempt will be made to indicate the lines along which the most important of these advanced while more detailed consideration will be accorded the development of pharmacology in another section of this article

The Development of Clinical Medicine

Through adopting the outstanding features of Hippocrates the father of medicine Sydenham 1624 1689 became the father of modern clinical medicine Observation and careful clinical records separated him from his fellow practitioners and resulted in the differentiation by him of diseases and the discovery of new diseases scarlet fever and chorea In therapy he was an empiricist but used great intelligence Progress may be made in three ways (1) careful histories of disease with according to him attempts at differentiation of essentials from the non essential features (2) fixed treatment founded on experience (3) searching out specifics in treatment

He gave a practical tendency to clinical medicine which has been retained to our day His teachings pervaded the whole realm of clinical

on his predecessors and contemporaries he is difficult to appraise To some he is a second *Hippocrates* to others a mere *blatant mountebank* But to Paracelsus or Valentine one or both medicine is indebted for its start along chemical lines

The four pillars of medicine according to Paracelsus, were philosophy anatomy alchemy and virtue From the noxious and indigestible the stomach separates the nutritious and digestible and utilizes it The physician must emulate the stomach Until he can find that which is chemically desirable his medicine will be a failure He believed that a specific remedy ' arcanum existed for every disease Simplicity in prescribing drugs was the natural result He abused the profession shamelessly for their absurd mixtures and concoctions for he also believed in the quintessence of drugs possibly a foreshadowing of active principles and alkaloids

To Paracelsus the world was a macrocosm all parts of which are represented in man the microcosm the most important constituents being sulphur mercury and salt Disease was chemical in origin Thus if the archeus of the stomach fails to separate the toxic from the nutritive or the excretory organs retain them we have the deposit of tartar on teeth in joints or as calculi in various other organs Tartaric diseases of Paracelsus were apparently the forerunners of 'lithemic diatheses

Antimony he introduced into medicine Tartar emetic was his favorite prescription So strongly did he champion it and so bitter was the opposition that at one time the University of Paris demanded from its candidates for the doctor s degree a pledge never to prescribe it

It must be admitted that Paracelsus was strong in his belief in the supernatural in magnetism in astral influences and in every other form of humbuggery known to mankind Similars sympathetic ointment and signatures permanently remove him from leaders such as Hippocrates Galen and Harvey Nevertheless he called attention to the importance of chemistry as the foundation for medical chemistry which however disproved most of the beliefs which he so loudly proclaimed

Van Helmont greatly imbued at first with the teachings of Paracel us studied alchemy in relation to medicine with the result that he discovered CO and proof of the existence of an acid in gastric digestion Through refutation of many of the fantasies of Paracelsus he did much to put medical chemistry and therapy on a sounder basis

The Beginnings of Scientific Medicine

With Harvey commenced experimental medicine Demonstration and proof were subsequently demanded words customs authority and

though a surgeon did much for diagnosis His interest in syphilis however was unfortunate His personal auto inoculation experiment though based on the sound principle of experimentation was premature and retarded progress for many decades so far as syphilis was concerned

Modern cellular vitalism was the gift of Rudolph Virchow It breaks up the old indivisible 'vital force' distributed throughout the whole body or located in a few organs into an infinite number of individual associated vital forces working together yet separately and assigns to them the elementary parts (which latter are considered to be cells) in definite microscopic seal Social arrangement or organization is beautifully conceived each part playing its own *role* influenced by others but performing its own function which in turn affects those of other parts

In the final analysis it is seen that the fundamental reasons for the lack of progress in medical treatment were (1) the inadequate state of science, *which made it impossible to cope with the complex problems of* the human organism of disease and of the processes of life and (2) the incorrect methods which were employed for approaching the subject theories and speculations predominating rather than observation and experimentation Our forefathers erred in accepting supernatural agencies as the basis of disease in employing remedies about which they knew but little for diseases about which they knew less and in not having true conceptions of either physiological or pathological processes Their fallacies resulted from dealing with ideas instead of facts

The introduction of the experimental method opened up new channels in medicine through which science has flowed in ever increasing volume The development of these so called underlying sciences has made possible scientific medicine

Present day Forms of Therapy

Rational Therapy

Rational therapy is a consummation devoutly to be wished—true rational therapy—treatment based on science and fact It includes all the elements necessary to success in the treatment of the individual case and for the progress of medicine at large It necessitates a correct diagnosis a grasp of physiologic pathology legitimate indications for treatment and the correction of deranged functions along rational lines The indications for rational treatment are derived from three sources

(*a*) *Etiology* —Removal of the cause constitutes radical treatment

medicine and were accepted and followed by Baglivi in Italy and Boerhaave in Leyden The former applying Sydenham s methods of observation differentiated fevers and described enteric fever which was prevalent in Rome and enlarged on the part played by tissues in disease He clearly outlined the clinical effects of coffee tea and chocolate and as a result introduced coffee as a cure for headache originating from fatigue Boerhaave though contributing nothing new inculcated these principles in the work of his students and became the greatest clinical teacher of his day

In 1761 Leopold Auenbrugger a young Austrian physician published a paper A New Invention for Discovering Obscure Thoracic Diseases by Percussion of the Chest Keen of observation he utilized inspection (noting lack of mobility) palpation and percussion and made many fundamental contributions to methods of physical diagnosis His work however attracted little attention until unearthed and reintroduced by Corvissart in 1808 Four years later 1812 Laennec introduced the stethoscope which tremendously increased the value of auscultation Thereafter clinical medicine was fully equipped with methods of physical diagnosis

Bruonianism —A new system of medicine was introduced in 1780 by Brown which was subsequently known as Bruonianism According to him Life is a state produced by excitability which is constantly being used and constantly replaced As in a furnace fire is life coal is excitability *the draft is the stimulus* Diseases result from too much or too little excitability and stimulus and are sthenic or asthenic accordingly Treatment consists of restoring the normal state of excitability by regulating the stimulus Drugs are stimuli and effectively regulate excitability in the following order opium camphor ammonia musk alcohol all of which are used in asthenic states On the other hand bleeding purgation cold low diet and passive exercise are debilitating and should be used in sthenic states Brown s treatment was extremely radical resulted in great injury and would have brought medicine into general disrepute had it been more generally adopted

Specialism —At this period physicians began to specialize in internal medicine * Prominent among them were Thomas Willis Sir John Pringle John Howard Wm Heberden John Fothergill James Parkinson Richard Bright and Edward Jenner of vaccination fame The names of Parkinson and Bright were attached to diseases they described In this development should be mentioned the great John Hunter who

* According to Garrison specialism existed among the ancient Babylonians there being a physician for each disease so that this movement must be looked upon as the revival of specialism

Symptomatic treatment is often the easiest for the doctor but injudiciously applied is responsible for most of the mistakes and many of the tragedies of practice

Empirical Therapy

This is based on clinical experience previous results serving as the guide the cause and mechanism involved and the reason for cure remaining obscure The term purely empirical carries with it a certain element of reproach The name has become a term of opprobrium While it is not the intent of the author to champion empiricism it should be remembered that experience is a good teacher and that the empirical treatment of one period has occasionally become the rational or specific therapy of a later date In a considerable number of instances clinical experience has furnished irrefutable evidence of the efficacy of the therapeutic measure long before the underlying cause and the character of the disease have been determined For instance mercury was used in syphilis and quinine in malaria before the treponema and the plasmodium were discovered while digitalis was used in the treatment of dropsy before the express relationship of dropsy to myocardial insufficiency was recognized In these and many other instances therapy has outdistanced the other branches of medical science a matter of commendation and not of reproach so far as treatment is concerned

Empiricism in therapy is permissible at times but only if the proof of its efficacy is convincing Inability to explain is admission of ignorance Empirical treatment may constitute the starting point of clinical investigation but invariably demands controls accurate observation of results effected critical judgment and simultaneously intensive search for the causal factors concerned Such scrutiny ofttimes reveals ineffectiveness whereupon the treatment must be abandoned

Supernatural Therapy

This is based on the primitive conception of disease and is perhaps the oldest of all forms of therapy It is primitive fundamental and fixed The credulity of the heathen amuses us in fact in our wisdom we smile Wherein does our own childhood teaching differ? It gives us faith and casts a cloak over reason Just as our Greek forefathers slept before the temples of Esculapius so we make pilgrimages to Rome or visits to the shrine of St Anne de Beaupre Absent treatment today is as effective as was the sympathetic ointment of Paracelsus Mental treatment suggestion and faith healing are unquestionably helpful at

and effects cures in conditions in which irreparable damage has not already resulted This is specific therapy the ultimate towards which all treatment strives Unfortunately its application is restricted owing to existing limitations in the science of medicine All too frequently the cause is unknown the mechanism and development of clinical manifestations obscure, conditions usually precluding specific therapy Nevertheless in this field, treatment has made great progress during the last decade

Specific therapy includes representatives of drug serum vaccine and organotherapy the group of diseases subject to direct control being constantly on the increase Thus we have quinine in malaria mercury and arsenic in syphilis arsenic and antimony in trypanosomiasis, specific sera for many infectious diseases desiccated thyroid in myxedema and pituitary extract in diabetes insipidus The chemical nature of some of the hormones has been determined a few have been isolated and in one instance namely thyroxin (the active principle of the thyroid) it has been actually synthesized and demonstrated to have all the effects of the desiccated gland With thyroxin metabolism can be profoundly affected Thus it is seen that specific therapy leads to fundamentals and will in all probability constitute the basis of the scientific treatment of the future

(*b*) *Pathology* —This is used in its broadest sense and includes functional and chemical as well as anatomical changes Certain pathological conditions are encountered clinically which demand a definite line of treatment irrespective of the underlying causes To be sure the cause may need treatment in addition Thus outspoken myocardial insufficiency calls for treatment per se independently of whether it is due to myocarditis secondary to syphilis rheumatism arteriosclerosis nephritis focal infection exophthalmic goiter or to some valvular lesion The underlying cause may also demand its own treatment simultaneously or at some subsequent time Similarly uremia calls for a certain line of treatment irrespective of whether it is due to nephritis polycystic kidneys or obstruction of the lower urinary tract and marked acidosis demands its own therapy independently of the underlying diabetes or nephritis

(*c*) *Symptoms* —Generally speaking symptomatic treatment should be avoided except as a last resort when other methods fail Symptoms are the expressions of deranged function and often blessings in disguise Their nature and cause should be determined Treatment should first be directed not to them but to their cause and to the correction of the deranged function This failing and particularly where the symptoms occasion great distress or endanger vital functions or life itself general measures for symptomatic relief may be adopted but the clinical investigation should continue and due caution be exercised that no harm is done

to a high tonus (or a high excitability) of the autonomic nervous system in one instance and of the sympathetic nervous system in the second Eppinger and Hess ( ) have made use of injections of these two substances for diagnostic purposes (2) Whether or not a function is disturbed or a lesion exists by giving drugs which accentuate or minimize the underlying defects thereby accentuating or removing the symptoms and signs In this connection (a) atropin and digitalis are utilized in relation to questions of conductivity and heart block atropin removing partial block and digitalis increasing it (b) Nitrites are used in questionable cases of mitral stenosis (3) Whether or not cure or specific reactions result from the use of specific remedies Thus in districts where malaria is prevalent fevers quickly subsiding on the administration of quinine are frequently accepted as malarial or vice versa Therapeutic tests are resorted to frequently where the existence of syphilis is in question

By such means diagnoses can be deduced at times Thus through knowing the seat of action it is possible to determine the functional state of the mechanism involved to bring out greater defects or to remove an etiological factor through the use of etiotropic remedies

Prophylactic Therapy

The miracles wrought by preventive medicine in the prevention of typhoid fever smallpox etc are made possible through immunity reactions and do not at the present time come in the province of pharmacology

On the other hand specific drug therapy has already achieved great results in relation to protozoal diseases and to local bacterial infections especially the venereal diseases Thus quinine is effective against malaria salvarsan against syphilis while mercury ointment prevents the development of syphilis and injections of protargol or argyrol the development of gonorrhea

Factors Responsible for Progress in Therapy

Having considered the factors which retarded the progress of therapy let us attempt to identify and analyze the factors responsible for the remarkable progress of recent years Innumerable influences have borne on the problem but the more important can be selected and analyzed Some of them are too broad to be dealt with other than in a general way while some which apply directly to pharmacology will be considered in more detail These factors may be enumerated as follows

times but their use should be supplemented by all that science and sound experience can furnish

Baseless Therapy

This is the 'therapy of fancy of Lauder Brunton Although medical science has caused the "old vessels which once held human beliefs to be abandoned therapy based on these beliefs still persists Often lack of time or ignorance prevents the busy practitioner from applying the four fundamentals of treatment Only too frequently the outstanding symptom is treated headache instead of uremia or loss of weight instead of diabetes

At times polypharmacy replaces pathology undiagnosed conditions being met by mixtures of drugs the action of any one of which is but poorly understood Fortunately the inclusion in the curriculum of medical schools pharmacology is rapidly doing away with this practice Perhaps more than any other factor the large pharmaceutical firms are responsible for the remnants of polypharmacy which still persist

Incredible as it may seem the therapy of many well trained physicians is directed not by their knowledge of the action of drugs but by the greed inspired claims of pharmaceutical houses Pamphlets dealing with theoretical and scientific considerations somewhat beyond the training of the average physician and outlining new discoveries of merit are placed in the hands of the practitioner for his seduction Because the information is new and smacks of science and because he fails to recognize fallacies in supposed correlations presented he is led into grievous error to wit the application of baseless therapy in the belief that he is treating his patient along approved modern scientific lines

Textbooks of therapeutics are the basis of much baseless therapy Authority that which dominated medicine from Hippocrates to Hunter is still effective The conscience of the physician is clear despite the disastrous outcome provided authority exists, i e the finger can be pointed to the printed page Fortunately the day of prescribing the name of a drug for the name of a disease is passing with the advent of modern works on pharmacology

Diagnostic Therapy

So certain and so well understood are the actions of certain drugs that they are used at times to assist in arriving at a diagnosis Thus it is possible to determine factors important in diagnosis (1) Whether or not a certain mechanism is hyper- or hypo active by observing the effect upon it of standard stimuli ' Believing that excessive reaction to pilocarpin on the one hand or to epinephrin (adrenalin) on the other points

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FACTORS RESPONSIBLE FOR PROGRESS IN THERAPY

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(1) The most important factor perhaps is the advancement of science generally Without science and its methods medicine would have remained an art

(2) The development of pharmacology whereby remedies whose actions are understood are directed to the correction of derangements in physiological functions

(3) The chemical basis of pharmacology, the recognition of the relationship of pharmacological action to chemical constitution of drugs and the development of remedies on this basis

(4) The development of specific chemotherapy and experimental therapeutics whereby remedies are scientifically developed and directed towards the removal of specific causes of disease

(5) The discovery of microorganisms and their relation to disease This is *directly responsible for the development of* bacteriology and immunology and for the development of preventive medicine the most important advance in medicine of all times It has also revolutionized surgical practice bringing all structures within the province of the operator through the application of aseptic and antiseptic principles

(6) Recognition of the role played in the organism by glands of internal secretion their relationship to metabolism and growth in health and disease and the development of endocrinology and organotherapy

(7) The adoption of a functional conception of disease with the consequent direction of treatment toward restoration of function

(8) Organization of *medical effort* (schools hospitals medical institutions and societies) and adequate channels of communication

An attempt will be made to outline the more important advances along these lines and the effects of each of these factors upon medicinal doctrines and practice Obviously it is impossible to do more than select outstanding examples in each field These will be dealt with in some detail however in order to reveal the development of principles

(1) Advancement of Science and Progress of Medicine

Progress has come through the advancement of science The Greek mind was active inquisitive and speculative the age dark scientifically though brilliant perhaps philosophically The Greeks had facts isolated but not correlated Experimentation was possible but lacking laws of science they could neither appreciate its value nor did they possess its methods

Let us visualize the difficulties confronting Hippocrates Let us suppose him confronted by a case of malaria The patient complains of chills, fevers sweats and aching in his bones and muscles Malaria has

never been described and none of his colleagues has ever encountered a similar case He studies the patient and confirms the temperature changes with his hands He offers a purgative or bleeds him and keeps him in bed The symptoms continue How can he proceed? Examination of the blood is impossible for he has no microscope and nothing is known of the character of the blood of corpuscles red or white or of plasmodia How is he to know that the mosquito has caused the infection? No one has discovered insects as carrier of disease How is he to know of cinchona which grows in far-off Peru Quinine has not yet been isolated Can he transfer the disease to animals Syringes have not yet come into existence experimental production of disease has never been attempted and the maltreatment of an animal might cost him his life Pathology is unknown and if in the event of death of his patient he obtains an autopsy he has no normal control What then must he do to get at the whole truth?

It would be necessary to (1) invent the microscope (2) invent methods of studying blood slides and establish the normal blood picture with which to compare the findings of his patient (3) discover the plasmodium of malaria (4) recognize mosquitoes as host and determine their role as hosts (5) prove the possibility of transmission from *mosquito to* man and work out *the life cycle of the plasmodium (6)* select cinchona from the thousands upon thousands of plant and in this particular instance it would have involved the discovery of the new world (7) isolate quinine for which procedure must be developed the science of chemistry (8) create protozoology and experimental pathology Since it has taken the best efforts of science and medicine twenty five centuries to accomplish these things we can scarcely hold Hippocrates responsible for failing to handle the case scientifically

Medicine is science and can only grow with science generally Hippocrates was honest Recognizing existing limitations he preferred not to go too deeply into the question of diagnosis but to treat the individual if not the disease to assist the vis medicatrix naturae We fail to recognize that the average citizen of today has a larger opportunity of casually acquiring medical science than was possible to Hippocrates through a long life of arduous labor

Lauder Brunton ([3]) writing in 1880 says Unfortunately we do not know medicine as we do chemistry and physics We have medical sciences for physiology pathology and pharmacology are justly beginning to lay claims to the title but medicine itself the recognition and cure of disease is still an art and not a science and as proof thereof he instances the same disease malaria We know that if a man pass through certain districts and more especially if he sleep in them he is

likely to be attacked with a fit of shivering which often lasting some time will be succeeded by a burning fever and then by profuse sweating after which he will feel comparatively well until the next day when another shivering fit will come on at the same hour and run the same course as the first. We know that by warning the man against the dangerous locality or by making him adopt certain precaution take cinchona alkaloids if he cannot avoid the place we may be able to prevent the disease by administering one large dose of quinine before the paroxysm we may stop its approach and by continuing the remedy we may prevent its recurrence altogether. But we are ignorant of the nature of malaria as we trace the course of these paroxysms whatever it may be. We do not know how it acts upon the bodily mechanism so as to cause them. We have no notion of the manner in which quinine counteracts the malarial effects.

And this was scarcely forty years ago. Physiology, pathology and pharmacology have more claim to the title of science now than then. Medicine itself, the recognition and cure of disease, is rapidly becoming science. The recognition and treatment of malaria is science—applied physiology, pathology and pharmacology.

Today we know the cause and the cure of malaria. Brunton * together with thousands of other physicians had at hand the instruments necessary for the solution of the problem in 1880. Hippocrates did not in 460 B.C. Both were equally honest in every respect. Each acted in accordance with his light, with the state of science and of cosmic consciousness.

But have we reached the ultimate in our conception of malaria and its cure? What is fever? What is a chill? Why does segmentation of the plasmodia result in fever? What relation have dehydration and sweating to chills and fevers? Is quinine necessary? What radicle of quinine is responsible for the destruction of the plasmodium and will it suffice? Innumerable questions confront us just as they did the Father of Medicine and Lauder Brunton. These, the future and science will solve. All medicine truly rational is science or fast becoming so.

(2) The Development of Pharmacology

Although drugs come down from antiquity the science, mechanism and seat of their action is of quite recent date. Bichat dissatisfied with the prevailing opinions of pathology and treatment devoted his short life

* These statements are not intended as derogatory to Sir Lauder Brunton. His name is mentioned in this connection first because of his pharmacological writings from which an excerpt is here presented and secondly because he represented the highest type of physician of his day and contributed abundantly to the sciences of pharmacology and therapeutics.

to the former Fired by his spirit his pupil Magendie took up his work and did for treatment what Bichat had done for pathology namely laid the cornerstone of an underlying science Perhaps more important than the results themselves were the methods of his experimentation His object was to determine the seat of the action of a drug Utilizing upas which contains strychnine he attempted to prevent it reaching the cord and again applied it directly finding in the first instance that it did not cause convulsions but that in the latter it readily did The first pharmacological experiment therefore was the demonstration of the action of strychnine on the cord

This appears a matter of simplicity today but was a new conception in Magendie's day *He first used upas subcutaneously getting convulsions in three minutes* The prevailing explanation concerning absorption and action of upas was that it was absorbed from the wounds into the blood was carried to the heart and thence to all organs including the nervous system where its special action was exerted It was in his method of proving this explanation that Magendie founded pharmacology He did not take it for granted he demonstrated and proved it As these constitute the first pharmacological experiments it seems advisable to present them

(*a*) *Channels and Rate of Absorption*—Injections into pleural and peritoneal cavities resulted immediately in the appearance of symptoms into an isolated loop of intestine after six minutes into a full stomach after one half hour Absorption occurred from the large bowel bladder and vagina but was slower as it was also from the stomach isolated by ligatures at the cardia and pylorus

(*b*) *Proof that Poison Acts Through the Circulation*—Injection into the jugular vein was much more quickly followed by convulsions than injection into the femoral arteries for in the latter the peripheral circulation must be made before the blood reached the heart and eventually the cord To rule out the so called sympathetic action suggested by his contemporaries he isolated the limb except for the blood vessels injected the drug and obtained the convulsions This experiment he repeated successfully after severing artery and vein and connecting their divided ends by goose quills He thereby ruled out lymphatics and nerves

(*c*) *Proof of Seat of Action in Cord*—Injections were made into carotid artery no convulsion resulting until sufficient time had elapsed for the drug to complete the circulation and reach the cord whereby the brain as the seat of action was ruled out The destruction of the cord by a probe prevented the appearance of tetanus dorsal cord destruction preventing tetanus of forelegs lumbar destruction tetanus of hind legs

Following the exposure of the cord by operation direct application to the cord caused immediate tetanus Thus for the first time was revealed not only the seat of action but also the channels of absorption and transportation and the mechanism of action

He next attempted to apply his discoveries clinically Nux vomica which was on the market acted much as upas and this he utilized in a case of paralysis with remarkably good results He found later however that it had already been used by M Fourquier but its use was based on Magendie s experiments

This remarkable investigation was followed by another by Claude Bernard ([4]) who was a pupil of Magendie Sir Benjamin Brodie ([5]) had demonstrated in 1812 that curare an arrow poison used by the Indians in the valley of the Amazon paralyzed voluntary muscles and that even after apparent death the heart continued to beat and the blood to flow as evidenced by the spurting of blood on section of an artery

Bernard took up the work in 1844 Three possibilities obtain an effect on the muscle itself on the peripheral nerve on the central nervous system The effect on the muscle itself could be ruled out by eliciting response by a galvanic current subsequent to curarization The absence of response in applying the current to the nerve located the seat of action in the nerve or muscle Was it nerve trunk or nerve ending? Muscles and nerve were soaked in a curare solution and it was found that on immersing the nerve trunk alone normal reactions followed stimulation whereas following immersion of the muscle no response could be elicited The seat of action therefore must be found in the nerve endings in the muscle Following this he demonstrated that the drug acted locally for after isolating the limb of a frog by ligation and injecting curare subcutaneously the ligated limb responded in normal fashion to stimulation despite the fact that the rest of the body was paralyzed

Little has been added to our knowledge of the action of curare since these experiments of Bernard To be sure Lauder Brunton subsequently showed the effect of curare on the cord itself and its slight effect in inhibiting conduction through sensory nerves The neural muscular junction has become somewhat better defined and we know that the nerves and end organs have no medullary sheath and hence are exposed to drug action The nerve end organs are complex structures containing nerve fibrils which pass into the true end organs or nerve plates which in turn send branching filaments into the muscle cells We know that curare interposes to centrifugal impulses resistance at a point below the nerve fiber and the actual termination in the muscle but the exact seat is still not known The union of curare with the nerve is chemical or

physico chemical in character the drug finally being freed and excreted if death has not supervened The curare action is due to the quaternary nitrogen group a property held in common with tetra methyl and tetra ethyl amines

Magendie and Claude Bernard inaugurated a new epoch in therapy Their investigations revealed the possibility of ascertaining accurate information concerning the seat and mechanism of action of drugs their methods constituting the foundation on which pharmacology now rests

Crum Brown and Fraser ([6]) in 1868 attacked pharmacology from a somewhat different point of view namely the relation of pharmacological action to chemical constitution Their work elucidated the subject of the anchoring of drugs by cells It was they who first determined the chemical character of curare They fixed the responsibility of its action on the quaternary nitrogen and proved that this action was held in common with all other quaternary ammonia bases Their claims were subsequently confirmed by Brunton and Cash Brunton devoted much time to pharmacology and scientific therapy investigating the action of an ordeal poison casca on the gastrointestinal tract heart and circulation and the action of digitalis on heart and circulation He also studied the diuretic action of digitalis On pharmacological grounds he introduced into medical practice the use of vasodilators

Schmiedeberg exercised a *profound* influence on the development of pharmacology to which he devoted his long life He introduced a new method of pharmacological study namely the action of drugs on the frog s heart which resulted in a much clearer conception of cardiac action and the influence on it of drugs In addition he also emphasized the chemical side of pharmacology and its relation to physiological chemistry discovering the synthesis of hippuric acid from glycocoll and benzoic acid and determining the formula of histamine and nucleic acid Above all else he influenced others his pupils perhaps more than any other group being responsible for establishing the science of pharmacology Hans Meyer of Vienna John J Abel of Baltimore and Arthur Cushny formerly of the University of Michigan now of London all leaders in the new science

In America pharmacology has made great strides Horatius C Wood ([7]) of Philadelphia a pioneer in this field bore the load single handed in the earlier days carrying out pharmacological and therapeutic researches on nitrites and hyoscine writing prolifically on all matters pertaining to the use of drugs and on many other fields of medicine With the coming of Abel and of Cushny chairs of pharmacology were created and its future in this country became assured

So rapid has been its progress that the action of drugs has been made

the basis not only of treatment but also of determining the state of activity of certain systems One example may be given which reveals in a remarkable way on the one hand the complexity of the mechanisms involved in physiological functions and on the other the exactness with which the seat of action of drugs can be determined

Through the researches of Gaskell Langley ([8]) and others much light has been shed upon the structure and functions of the sympathetic nervous system Although it presides over many of the vital functions the importance of its role has but recently been ascertained In disclosing these revelations drugs have been of the greatest assistance and have resulted in the use of the so called pharmaco dynamic tests

In opposition to the animal nervous system which is under the control of the will, stands the vegetative system ([9]) through the efferent branches of which are supplied organs whose function is not so controlled The vegetative system consists of two varieties of nerves the sympathetic and the autonomic or craniosacral (Fig 1) Almost all the internal organs are supplied by fibers from each class which act antagonistically thereby resulting in tonicity of a smooth muscle and normal function of glandular structures

Excessive activity on the part of either system results in a rather characteristic train of manifestations Since their actions are antagonistic stimulation of one system produces effects analogous to inhibition of the other The vegetative system as a whole is influenced by nicotine which at first stimulates and later paralyzes all its ganglia and post ganglionic fibers On the other hand certain drugs affect only one system or the other Thus epinephrin acts only on the sympathetic nerve endings exciting them and hence produces the same effect on the various organs as stimulation of their sympathetic nerve supply Epinephrin therefore causes vasoconstriction (coronary and pulmonary excepted) strengthening and accelerating the heart dilating the pupils and increasing secretion of the salivary glands while on the functions of the stomach intestines and bladder, where the sympathetic normally inhibits it causes relaxation

Certain other drugs affect the autonomic exclusively without influencing in any way the sympathetic system The drugs acting on the autonomic system are atropine which paralyzes it and pilocarpin and muscarin which stimulate it Thus muscarin and pilocarpin cause miosis slowing of the heart contraction of bronchial muscles violent contraction of the intestine and secretion of true glands while atropin in each instance causes the reverse of these effects

By the therapeutic application of epinephrin atropin and pilocarpin much can be learned concerning the functional state of mechanisms

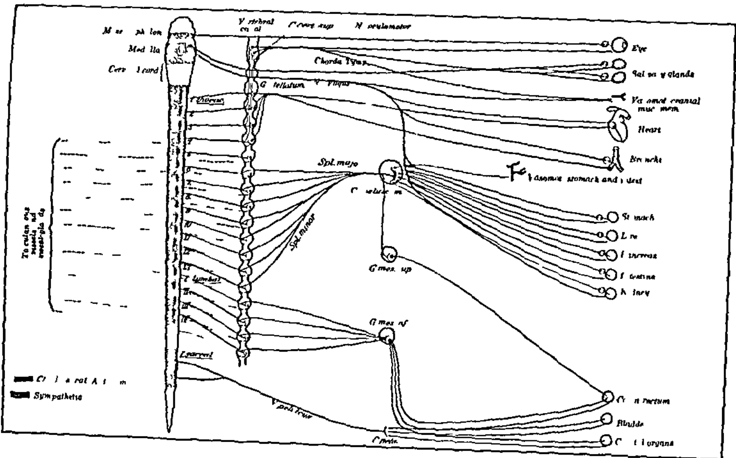


Fig. 1

Diagram of the Autonomic or Vegetative Nervous System. The Sympathetic Innervation is in Red and the Craniosacral Autonomic in Blue.

(After H. H. Meyer and R. Gottlieb, Die Experimentelle Pharmakologie, published by Urban & Schwarzenberg, Berlin.)

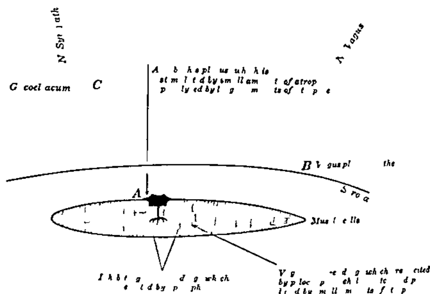


FIG 2 DIAGRAM OF THE INNERVATION OF THE INTESTINE

After Meyer and Gottlieb Die Experimentelle Pharmacologie
Urban and Schwarzenberg Berlin

innervated by these systems Through their use the responsibility of sympathetic or autonomic systems for certain manifestations can be determined According to the preponderance of the sympathetic or autonomic systems generally individuals are classified as sympatheticotonic or vagotonic It is true however that these pharmacological facts have led to speculations in clinical medicine which on the whole have caused confusion rather than clarity

The effects of these drugs can best be exemplified by consideration *of their action on the muscles of the intestine Movements of the intestines* are of three kinds (a) pendulum which results in division mixing *and moving about of intestinal contents (b)* true peristalsis with contraction above and relaxation below the result of distention or chemical stimulation resulting in the moving downward of the intestinal contents and (c) rolling movements violent contractions of the small intestine involving considerable stretches of it described by Meltzer and by him ascribed to increased vagus tone with simultaneous inhibition of the splanchnic sympathetic These movements are under the control of Auerbach s plexus or Langley s enteric system stimulation coming through the vagus and hypogastric and inhibition through the *splanchnics (Fig 2)*

Drugs which act upon the autonomic and sympathetic systems markedly affect intestinal movements pilocarpin muscarin and physostigmine stimulating contraction which may be violent and tonic in character and atropin inhibiting contraction through paralysis of the vagus terminals These results are effected by direct action on the vagus terminals and not through Auerbach s plexus and the sympathetic terminals Auerbach s system is composed of branches from the vagus and sympathetic and acts automatically and independently On stimulation it accelerates and strengthens normal waves of contraction but does not result in tonic contractions or cramps On this plexus atropin exerts in small doses at first a stimulating and later in larger doses a paralyzing effect just as do nicotine and strychnine

The sympathetic system is the inhibitor acting antagonistically to the plexus and to the vagus nerve It is subject to stimulation by nicotine and epinephrine *both of which cause relaxation of* the intestinal wall The innervation of the muscles together with the seat and character of the *action of various drugs are graphically depicted in Fig 2*

The action of atropin is interesting because of the existence of two points of action Thus therapeutically it may cause *either relaxation* of spasm or increased normal peristalsis depending on the condition of tonicity obtaining at the time of administration In lead poisoning and vagotonia for instance where tonicity is greatly increased through

stimulation of the vagus atropine causes relaxation through its action on the vagus Through the relaxation of spasm normal intestinal movements and activity supervene In this manner atropin may act as a purgative or a supplement to other purgatives in the conditions of increased intestinal tonicity resulting in constipation On the other hand administered when increased tone or spasm is absent atropin tends to increase peristalsis through its influence on Auerbach s plexus Thus is explained pharmacologically a fact long recognized clinically namely that belladonna or atropin in small doses are valuable in conjunction with purgatives in some spastic types of constipation In large doses they paralyze the intestines The dose therefore must be adapted to the existing condition and must remain small if intestinal peristalsis is desired

(3) The Chemical Basis of Pharmacology *

One approaches this subject with trepidation, yet with hope Much is known in a fragmentary way there are isolated instances of the effects of constitution on pharmacological action Definite laws can be laid down in some instances as to the character of changes in action resulting from changes in constitution along determined lines Still in a broad practical sense but little is known about it at the present time We have but a vision of the "promised land"

As the atom and molecule are fundamental to the understanding of chemistry so cell and molecule are fundamental to chemotherapy In the progress of science naturally form received attention first later function and lastly constitution and chemical reactions The body consists of cells of different sizes shapes and groupings all of which are affected by disease The cells perform functions of diverse nature in relation to which there exists great interdependence of activity Their functions are also affected by disease The cells live Their life depends upon chemical activities and the function is associated with or controlled by chemical reactions and these in turn are affected by disease

From the standpoint of chemotherapy the living cell and the chemical molecule are brought into relation The cell must be looked upon as a participating seat of microchemical reactions In it are chemicals undergoing reactions resulting in the development of forces to it are being added constantly new chemicals resulting in modification of reactions and of forces Products result which are valuable to the cell and hence are

* Two excellent works exist on this subject Die Arzneimittel Synthese by Sigmund Frankel Julius Springer Berlin 1906 and The Chemical Basis of Pharmacology by Francis and Fortescue Bricksdale Edward Arnold London 1908

retained or to other cells when they are transported elsewhere or which are simply by products or end products in which event they are thrown out from the cell for excretion The living cell is a series of electric cells or a laboratory in which reactions are going on constantly and in which forces are being created The medicament is a new chemical reagent and the effect of these new chemical molecules on the natural process is the factor to be determined

In order to obtain a comprehensive grasp of these activities of a cell and of the effect of new extraneous chemical molecules upon them it is necessary to understand both factors namely the constitutional reactions and normal activity of the cells on the one hand and on the other the constitution and relationships of the new chemical molecule added

The key to pharmacological action of a drug is found in the chemical constitution and activities underlying and associated with cell function Unfortunately this is where medical science is lacking Knowledge of the ultimate physics and chemistry of cells is wanting Consequently at present investigation in chemotherapy is limited in character permitting only modification relative to the extraneous chemical molecules and the study of the effects of these changes in modifying gross physiological functions

From the foregoing it is obvious that in order to act upon the cells contact or incorporation is essential In this connection Ehrlich (°) has emphasized the importance of distribution of chemicals and in the same connection has introduced his conceptions which involve chemo ceptors The distribution varies with different drugs and is more or less accepted by the profession as a matter of course On the other hand it constitutes a vital process which is a determining factor in pharma cological action Localization seat of action and channels of excretion are not matters of chance but are determined by the chemical constitution of the medicament In order that a drug may act on the cell it must be anchored by a receptor

Cells possess receptors of several types nutritive ceptors chemo ceptors and immuno ceptors Foods drugs and toxins contain hapto phore groups which in the event they fit the receptors attach the molecule to the cell But some differences exist in the mechanism involved with *these varying substances The nutritive molecule is assimilated by the* cell The molecule of toxin is capable of setting up processes of immuni zation which result in excessive production of receptors which are thrown off into the circulation where they constitute antibodies capable of uniting with and rendering inert the toxic molecule Chemoceptors unite with haptophores of drugs and thus render them capable of action

but they are not found as a rule in excess that is they do not exist as antibodies free in the circulation It also appears that the receptors may be only partially occupied by the drugs in which condition they are still susceptible to union with closely allied drugs i e atoxyl and arsenious acid Thus a trypanosome may be resistant to atoxyl and its affinity for arsenic blunted yet if it be subjected to a surcharge of arsenious acid it is affected It is possible in other instances that some radicle or side chain constitutes the haptophore group and is responsible for fixation as for instance the acetyl group (CH_3CO) in arsacetin which renders the latter effective in atoxyl fast strains *On the other hand receptors* may be completely fixed by one drug and also by closely allied drugs, for instance trypanosomes made fast for both atoxyl and arsenious acid may be fast also for antimony

The physical and chemical properties of the cell and of the medicament determine the presence or absence of affinities The nature of these affinities or receptors is important The variants must be considered (*a*) the chemical and (*b*) the protoplasm of the cell the relation being mutual or reciprocal

(*a*) *Chemical Factors*—From the chemical viewpoint many factors must be considered Variation in valence markedly affects the chemical properties The fundamental observation in Ehrlich s work consisted in recognizing that it was trivalent and not pentavalent arsenic which destroyed trypanosomes The striking difference in the toxicity of Hg_2Cl_2 *and* $HgCl_2$ *and of* CO_2 *and* CO *affords ample proof of the* importance of valence

The chemical constitution or formula is another determining factor Knowledge of the empirical formula is necessary but does not suffice Complications arise in the possibility of different arrangements of the atoms in the molecule Thus two substances may have the same empirical formula the same number of C H and O atoms but yet be different in every respect Thus $C_2H_4O_2$ represents acetic acid but it also represents formic ester two very different substances Chemistry teaches us that C_3H_8O may represent two substances $OHCH_2CH_2CH_3$ normal propyl alcohol or $(CH_3)_2CH\,OH$ isopropyl alcohol and that these substances have different chemical and physical properties Properties depend on chemical grouping within the cell so that knowledge of structural formulae is also necessary

Pasteur demonstrated that there were several kinds of tartaric acid $C_4H_6O_6$ dextro laevo meso and racemic He demonstrated that atoms may have different space arrangements and in so doing he founded stereoisomerism The stereoisomeric arrangement also markedly affects chemical and pharmacological properties As the molecule of hydro

carbons increases in size and the complexity multiplies the possibilities for different substances increases tremendously thus $C_{13}H_{28}$ offers more than 800 possibilities Consequently the difficulty of assigning constitutional formulae has become increasingly great But structural formulae are essential as the basis of study of pharmacological action Radicles play a great role as haptophores or as powers affecting chemical reactions Affinities are constitutional properties in the terms of Ostwald

Solubility is of the utmost importance Toxicological measures frequently consist of attempts to render solutions of drugs insoluble and antidotes frequently owe their efficacy to their power of precipitating the poison before its absorption Unless in solution incorporation in the cell is most difficult Incorporation is necessary for action

The methods of administration of certain drugs are determined by the factor of volatility thus chloroform and ether owe much to their volatility which permits a ready means of administration and also considerable control

(*b*) *The Protoplasm of the Cell*—The chemical structure of the molecule of most drugs is simple compared with that of the cell It is the protoplasm of the cell that offers the chief difficulty in solving the problem of the action of drugs Proteins are so infinitely complex that attempts to consider them chemically are not profitable at present The chemistry of the living cell is beyond the science of today At present however our main interest centers on the living cell and particularly on the properties of cells which make them subject to influence by drugs What constitutes the chemoceptors? A silk fiber stains with picric acid a nerve fiber takes up methylene blue intravitam a certain nerve responds to an alkaloid Ehrlich discards the possibility of surface attraction and of absorption in staining of fibers and limits consideration to two factors (a) insoluble salt combinations as advanced by Knecht and (b) solid solutions of van t Hoff as outlined by Witt In the first instance lanugic acid from wool fiber and nucleic acid of nuclear substances may precipitate basic dyestuff from solutions Methylene blue as a vital stain is thus thrown down by the plant as the insoluble tannate An example of solid solution is seen in silk stained with rhodarium which fluoresces This must be a solution since rhodarium is not fluorescent except in solution It is assumed therefore that the dye forms a homogeneous mixture with the silk fiber i e it is in the form of a solution The same dye often produces different tints in various kinds of fibers This is analogous to the fact that the same substance often dissolves in different solvents in entirely different tints'

The factors which determine the formation of the dye are properties of both the drugs and the cell Mutual relationships must exist It is impossible to separate them absolutely as factors apart since mutual forces are encountered in the drugs and in the cell

(*a*) *Colloidal State* —What relationships exist in the living cell? In gelatin there are vesicular and sponge like gels' In the former the liquid phase exists in the form of separate droplets each surrounded by a continuous film of solid phase In the latter, the two phases are reversed the solid phase is in the form of a network of threads while the liquid phase is continuous The former is the ordinary gel from which fluid can be expressed only with the greatest difficulty the latter obtained through the action of formaldehyde is a gel from which water is readily expressed This problem has been elucidated by the system of solvents so nicely demonstrated in the work of Clowes Bayliss ([11]) who says "Protoplasm in the living state has the properties of a liquid system containing however particles of solids and amounts of immiscible liquids in a freely moving state' The relationship of dyes and drugs to the various phases must enter into consideration of pharmacological action

(*b*) *Surface Condensation or Adsorption* —The structure of protoplasm is such as to present large surfaces which furnish excellent ground for the play of surface forces so important in life processes Drugs may be held in contact with cells by adsorption

(*c*) *Changes in Cell Membrane*—The surface layer of cells frequently present relatively limited permeability through which the cell is protected from other cells and from surrounding fluids The character of this membrane and its permeability plays a role in the action of chemicals Solvents of this membrane make ingress possible

(*d*) *Velocity of Diffusion* —The passage of substances into a cell must be considered a factor in some instances Thus Straub showed that muscarin in the heart of aplysia had no effect when the concentration within the cell reached the concentration outside of the cell Only during the period of concentration in the cell was the drug active Naturally in addition the physical and chemical properties such as solubility, volatility surface condensation or adsorption and electrical charges are important

Velocity of diffusion solubility and volatility of drugs colloidal states surface condensation and electric charges of both drugs and cells all play a role in determining fixation rate of absorption physiological action and excretion of the drugs by the cell

The cell protoplasm plays a great role in solubility and hence in

making substances available The narcotic value of a drug depend principally on its solubility in lipoid substances Generally speaking the most powerful narcotics are those which are most soluble in oil and least soluble in water Lipotropic substances are also neurotropic The Overton Meyer theory of narcosis attempts to explain the entrance of drugs to the nerve cells on this basis They gain access to the cells of the cerebral nervous system owing to their solubility in cell lipoids in which these cells are particularly rich Gradations in narcotic power are due to the presence of groups which increase the partitive coefficient i e which render the derivatives more soluble in such fatty substances Physical as well as purely chemical factors play a role In the cell proteins lecithins salts and water exist in a physicochemical combination and the drugs affect this physicochemical equilibrium This conception is constantly attracting more attention A chemical may be anchored to a cell very quickly yet it may not manifest its effect immediately for instance tetanus toxin is anchored eight minutes subsequent to intravenous injection at which time antitoxins are usually ineffective and fail to protect though given simultaneously with the toxin they protect perfectly

These theories explain the presence of the drug in the cell but not its mechanism of action According to Oscar Loew general poisons react on protoplasm in four ways oxidation catalysis salt formation and substitution

The first includes oxidizing agents such as H_2O_2 and ozone permanganates etc The catalytic agents are represented by the aliphatic narcotics Iodine in relation to metabolism is considered by some to act as a catalizing agent only Salt formation is dependent upon the amphoteric character of protein and involves acids bases alkaline earths and salts of heavy metals The fourth group includes a large number of substances capable of reacting with aldehydes and amines such as hydroxamines phenyl hydroxamines hydroxylamines anilines free ammonia phenols especially the amido phenols and HCN and H_2S

Amines particularly are active primary amines other than of the aliphatic series being more active than secondaries which in turn are more active than tertiary Thus NH_2 groups are important radicles in basic dyes OH in acid dyes where they are known as auxochromes These active radicles react with labile groups of living protoplasm and thus affect the living cell These labile groups disappear with the death of the cell subsequent to which such reactions cease Loew believes that toxicity increases *pari passu* with reactivity

Ehrlich launches many arguments against synthesis in cells and

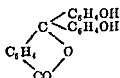
states that in his belief, it rarely occurs in relation to substances foreign to the cell He admits however that it does occur in relation to vinyl amine which produces a peculiar papillary nephritis, an ethyl amide group entering the protoplasmic molecule

Specific or special poisons act only on certain classes of organisms In this group he considers toxins and antitoxins specific poisons alkaloids and indirect poisons which interfere with oxidations such as HCN In the mind of the writer no reasons exist for placing alkaloid and specific poisons in this special class

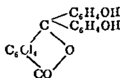
In selective action two factors naturally suggest themselves, namely (a) reactions which play such an important role in relation to staining and acid and basic dyes and (b) the degree of oxygen saturation Unquestionably these are determining or at least secondary factors in many instances

In relation to pharmacological action and absorption and excretion it is interesting to revert to an observation made by Ehrlich and which he refers to repeatedly i e that the sulphonic group introduced into neurotropic substances renders them inert from the point of view of the nervous system The introduction of a sulphone group SO_3H (=SO) renders many substances inert, i e it changes the distribution of the drug in the organism

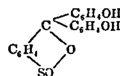
Sulphonation also plays a role in relation to excretion of drugs. Thus phenolphthalein $C\ H_{14}O_4$



when introduced into the body is excreted by both liver and kidneys If chlorine is introduced in the phenol rings ([1]) ([13])



it is excreted entirely by the liver If on the other hand it is sulphonated ([14])



it is excreted entirely by the kidneys Sulphonation therefore has resulted in a different channel of excretion and in one of the most striking instances of specificity known to medical science Sixty to eighty per cent of the drug on intravenous injection is excreted in one hour by the normal kidney In this connection a striking affinity exists for the dye by the renal cells so striking that practically all of the dye is taken up by the kidney in the cour e of an hour But the dye is not fixed Here then we have an affinity without action on the cell the drug being picked up and excreted The explanation is difficult Unquestionably many other similar instances exist in relation to ex cretion

Instances of Chemical Constitution Controlling Pharmacological Action

In 1859 Stahl chmidt ([15]) demonstrated that strychnine loses its tetanizing action when a methyl group is introduced and the new com pound assumes a curare like action Crum Brown and Fraser in 1868 in view of the ammonium base formed in this reaction investigated other similar bases derived from alkaloids brucine morphine and thebaine and discovered that all quaternary ammonia bases exert a curariform action paralyzing motor nerve endings This was the be ginning of rational synthetic pharmacology and called attention to the relation of pharmacological action to chemical constitution

Ehrlich ([16]) in 1898 enumerated five important instances selected from the whole field of therapy where a relationship was established between chemical constitution and pharmacological action (1) The antipyretic action of aniline and amido phenol derivatives is definitely related to the amount of pure amido phenol (NH_2C H OH) split off in the organism Prevention of the splitting off of this substance by sub stitution as in amido acetophenon (NH_2C_6H $COCH_3$) renders the sub stance ineffective as an antipyretic

(2) Antipyretics become ineffective through the introduction of salt forming acid radicles such as SO_3H and CO_2H Thus the antipyretic action of acetanilid C_6H $NHCOCH_3$ is destroyed by the introduction of acetic acid CH_3COOH which results in C H $N(COCH_3)CH$ CO H Similarly the sulphone derivative $C_6H_5NHCOCH_2SO_3H$ no longer af fects temperature Phenacetine



likewise is no longer an antipyretic if sulphonated or carbonated The reason for this is found in the prevention of splitting resulting in free p amido phenol

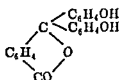
states that, in his belief, it rarely occurs in relation to substances foreign to the cell. He admits however that it does occur in relation to vinyl amine which produces a peculiar papillary nephritis, an ethyl amide group entering the protoplasmic molecule.

Specific or special poisons act only on certain classes of organisms. In this group he considers toxins and antitoxins, specific poisons, alkaloids and indirect poisons which interfere with oxidations such as HCN. In the mind of the writer, no reasons exist for placing alkaloid and specific poisons in this special class.

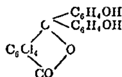
In selective action two factors naturally suggest themselves, namely (a) reactions which play such an important role in relation to staining and acid and basic dyes, and (b) the degree of oxygen saturation. Unquestionably these are determining or at least secondary factors in many instances.

In relation to pharmacological action and absorption and excretion it is interesting to revert to an observation made by Ehrlich and which he refers to repeatedly, i.e. that the sulphonic group introduced into neurotropic substances renders them inert from the point of view of the nervous system. The introduction of a sulphone group SO_3H (=SO) renders many substances inert, i.e. it changes the distribution of the drug in the organism.

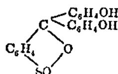
Sulphonation also plays a role in relation to excretion of drugs. Thus phenolphthalein $C\ H_{14}O_4$



when introduced into the body is excreted by both liver and kidneys. If chlorine is introduced in the phenol rings ([1]) ([13])



it is excreted entirely by the liver. If, on the other hand, it is sulphonated ([14])

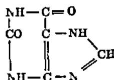


Aliphatic Hydrocarbons

Lauder Brunton called attention to the fact that the action of the aliphatic series is chiefly on nerve centers first stimulation then narcosis and predominantly on sensory nerves The lower members of the fatty series especially are preponderantly stimulating and anesthetic to nerve centers Schmiedeberg recognized two classes (a) the alcohol and chloroform group which includes most of the narcotics of the aliphatic series gaseous and fluid hydrocarbons the monatomic alcohols their ethers ketones aldehydes and their halogen derivatives (b) the ammonia derivatives which exercise a convulsant action on the cells of the cord Conversion from trivalent to pentavalent nitrogen is accompanied as already stated by marked changes in physiological effect a curare like action replacing the convulsant

The introduction of alkyl groups into aliphatic compounds generally increases the physiological effect But as the molecule increases the solubility and volatility decreases and the compound becomes relatively inert As a rule substitution of the H of the hydroxyl by an alkyl group results in an ether an entirely different substance with different properties and increased volatility Under such conditions ethyl alcohol is converted into ethyl ether $C H_5OC H_5$ while glycerine becomes the glycerine ester which has narcotic properties On replacing the H atom of ammonia with alkyl groups amines (primary secondary and tertiary) result with decreased toxicity but as the tertiary amines are converted into ammonium compounds the toxicity is markedly enhanced An alkyl group entering a carboxyl group converting the organic acid into an ester naturally confers new properties thus oxalic acid yields the narcotic di ethyl oxylate

The ureids are important in the animal economy and in therapy Uric acid represents dibasic ureids the end stage of nuclear metabolism Xanthine



one of the intermediate products is somewhat inert By the introduction of methyl groups one two or three into the amide radicles new pharmacological properties appear Thus we obtain theobromine



which is essential for antipyretic action

(3) In the pyridin series, C_5H_5N, the hydrated products act more strongly than the parent substances

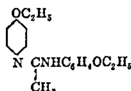
(4) The benzoyl radicle (C_6H_5CO) is the anesthesiophore group of cocaine and many of its substitution products Cocaine $C_{17}H_{21}NO_4$ breaks up on hydrolysis as follows



$$C_{17}H_{21}NO_4 + 2\ H_2O = C_9H_{15}NO_3 + C_6H_5COOH + CH_3OH$$

If the ecgonine methyl ester is substituted by other radicles than benzoyl for instance succinic acid ($C_4H_6O_4$) the resulting chemical has no anesthetic properties Substitution leaving the benzoyl radicle intact has been the basis of many of the cocaine substitutes

(5) Recognition of the relation of ethyl groups to hypnotic action of drugs resulted in the preparation of more effective hypnotics The more ethyl groups in di sulphonic bodies the more active becomes this property In sulphonal there are two (CH_3) C ($SO_2C_2H_5$)$_2$ and in trional three $CH_3(C_2H_5)C(SO_2C_2H_5)$ They are also present in amylene hydrate and ethyl urethane The ethyl group is also active in phenacetine $C_6H_4OC_2H_5NHCOCH_3$ in holocaine



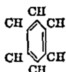
Thus alcohol itself exerts a soporiferous action as do the alcohol radicles in various hypnotics sulphonal, trional amylene hydrate and in certain anesthetics

Obviously, it is impossible to more than touch upon certain rules or generalities * relating to the subject The aliphatics as a group are not as active pharmacologically as the aromatic hydrocarbons which are also in addition more reactive from the chemical point of view

* For detailed discussion of the chemical basis of pharmacology the reader is referred to the excellent volume of Francis and Fortescue Bricksdale which is the best publication of its kind known to the writer From it are taken many selected examples of the relation of pharmacological action to chemical structure here presented

character of the substance thus salicylic acid becomes the methyl ester methyl salicylate or oil of wintergreen Phenols become inert ethers Substitution may occur in the H atoms of the ring or in the groups which substitute H Kendricks and Dewar laid down a rule that the introduction of H into cyclic bases invariably increases pharmacological action and toxicity Dujardin Beaumetz and Bardel studied the influence of side chains on benzene compounds and concluded that (a) those with OH are antiseptic, (b) those with amide or acid amide groups are hypnotic (c) those containing both an amide and alkyl group are analgesic These rules must not be taken as absolute but they hold in the majority of cases and constitute an intelligent basis for changes in structure

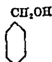
The influences of certain changes in relation to benzene seems perhaps as well as any other example to demonstrate the effect of structure on function



(benzene) produces somnolence and lethargy



(toluene) is antiseptic,

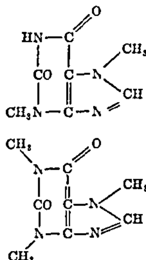


(benzyl alcohol) is a local anesthetic



(phenol) has acid properties and is antiseptic and toxic,

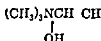




and caffeine

both of which are excellent diuretics and cardiac stimulants

Unsaturated open chain hydrocarbons are more toxic than the saturated and are extremely reactive The double bond offers enlarged opportunities for reaction Toxicity is multiplied many fold To this class belongs neurine



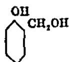
a dehydration product of cholin, which is itself not markedly toxic

Aromatic Hydrocarbons

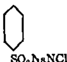
Generally speaking these are more reactive have more marked pharmacological action and tend as pointed out by Brunton to affect motor rather than sensory nerves and to produce convulsions and paralysis Benzene acts on cerebral centers producing somnolence and also paresis of muscles and tremor Diphenyl and its compounds tend to be more inert Napthalene is relatively more toxic and is said to slow respiration and decrease metabolism

Substitution of H of the ring nucleus of benzene by alkyl groups tends to decrease reactivity and toxicity and to modify pharmacological properties In anilines it increases toxicity while in phenols it increases the antiseptic value and decreases toxicity Alkyl substitution of the OH of phenol renders the new compound practically inert while the same procedure in resorcin results in increased toxicity Alkyl substitution in the NH_2 group of anilines depresses the convulsant action whereas in benzamides and salicylamides it increases it Alkyl substitution in the carboxyl chains of aromatic compounds changes the

marked Salicin, $C_{13}H_{18}O_7$, yields on hydrolysis a glucoside and saligenin



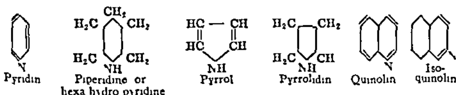
(saligenin) is a local anesthetic with one half the toxicity and twice the anesthetic effect of benzyl alcohol according to Hirschfelder



(benzene sodium sulpho chloramine or chloramine B) in which the NCl group is held responsible for its marked antiseptic property

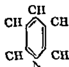
Heterocyclic Hydrocarbons and Alkaloids

The important members of this group are



These enter into the consideration of the chemistry of alkaloids and therefore are of great medical interest

Pyrrol somewhat resembles benzene in its action Pyridin is the nucleus thus



and is least toxic while piperadine and pyrrol and pyrrolidin are more active The larger the chain the more active the compound as a rule The entrance of an alkyl group definitely increases activity tetra methyl pyridin being several times as potent as pyridin itself and exhibiting somewhat different action Quinolin is closely related to pyridin

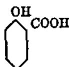
Alkaloids are complex nitrogenous substances with basic properties possessing a pyridin or a condensed pyridin nucleus

Atropine $C_{17}H_{23}NO_3$

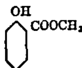
(cresol) the substitution here has increased the germicidal efficiency, while the toxicity is not increased at least not in the same ratio Cresoles possess advantages as antiseptics



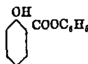
(benzoic acid), is non toxic and slightly antiseptic,



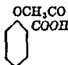
(salicylic acid) is mildly toxic antiseptic and has specific properties against streptococcus infection (fever pain) the corresponding meta and para derivatives having neither of these properties,



(methyl salicylate) has the same general properties as salicylic acid Substituted methyl radicles yield other substances with similar properties, methyl oxymethyl (mesotan) mono glycol (spirosal)

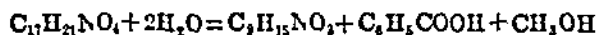


(salol) Such phenyl salicylates on decomposition yield active phenols for local action Consequently their use has been attempted as intestinal antiseptics Instead of the phenyl group, naphthyl may be substituted



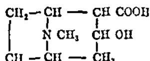
(aspirin) has the same general effect as salicylic acid but the analgesic and antipyretic effects are greater and the local irritating effect is less

(benzoyl ecgonium methyl ester) On hydrolysis it splits up into a base ecgonine methyl alcohol and benzoic acid



$$C_{17}H_{21}NO_4+2H_2O=C_9H_{15}NO_3+C_6H_5COOH+CH_3OH$$

Ecgonine as already stated is closely related to tropine and has the formula



The most important pharmacological attribute of cocaine is its power of producing analgesia and anesthesia This is not due to the ecgonine group but usually to the presence and relative position of the two substituting groups The (CH_3COO) group is essential to the action of cocaine as activating the carboxyl group The importance of the benzoyl group is shown by the fact that in its absence no anesthetic effect occurs and moreover many other substances containing it exert the same effects In ecgonine derivatives it cannot act without simultaneous replacement of the carboxyl group by a COOR group and the presence of the two groups alone in such a simple substance as benzoic methyl ester $C_6H_5COOCH_3$ is sufficient to produce local anesthesia

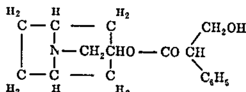
As already indicated Ehrlich referred to the C H CO group as the anesthesiphore radicle The N(CH_3) group is an auxotox and on it depends the liver degeneration Thus it is possible to analyze cocaine into its more important radicles and to explain rationally its various properties on the grounds of its chemical constituents

Opium Alkaloids—Opium contains several alkaloids the more important being morphine papaverin codeine narcotine narcine and thebain Their properties have been known for a long period Recently through the work of Macht ([17]) our knowledge of their nature mechanism and cause of action has been greatly enhanced

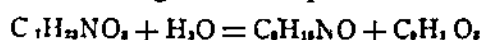
Macht began his studies by investigating the action of the opium alkaloids individually and in combination with each other on the respiratory tract He demonstrated (a) that on the bronchi narcotine and papaverin are dilators as are also morphine and codeine but to a less extent The other alkaloids have no such effects Morphine and narcotine act antagonistically (b) that morphine and codeine are sedative or depressant while narcotine papaverin narcine and thebain are stimulating to the respiratory centers and (c) that the combined action of opium alkaloids is a combination of their individual effects

He later studied quantitatively the analgesic effects of the six principal opium alkaloids and found the effective dose to be morphine

Atropine,

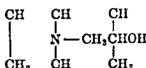


is an ester When hydrolized it yields tropine, a condensation of piperadine and pyrrolidin rings and tropic acid

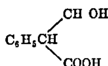


$$C_{17}H_{23}NO_3 + H_2O = C_8H_{15}NO + C_9H_{10}O_3$$

Tropine has the formula,

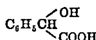


tropic acid,



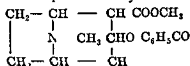
Tropine differs from ecgonin by one carboxyl group (*vide infra*) consequently, atropin and cocaine are very closely related chemically As a matter of fact they give almost identical constitutional effects so far as cerebrum heart (vagus terminals) temperature blood pressure and eyes are concerned Atropin however paralyzes the nerves to unstriped muscles and secreting glands while cocaine has a more marked anesthetic effect and causes in addition peculiar foamy degeneration in the liver cells of mice first recognized by Ehrlich

The substitution of other acids for tropic acid may be made resulting in other tropines Thus homatropin is a tropine of mandelic acid

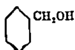


The relation of tropic and mandelic acid is evident The more rapid onset and the shorter duration of action of homatropin is due to more rapid absorption and excretion

Cocaine C_{1} H ,NO_4 is represented by

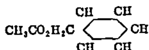


Recognition of the role played by the benzyl group in the relaxation of unstriped muscles led him to further investigation of the properties of the benzyl nucleus and to the discovery of its value as a local anesthetic Benzyl alcohol or phenmethylol has the formula C_7H_8O or

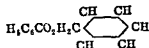


In nature it occurs in jasmine and as an ester in the balsams of Peru and of Tolu Compared with the well known local anesthetics it possesses powerful local anesthetic properties and at the same time is relatively non toxic Clinically in one to four per cent solution it is an effective safe local anesthetic

The esters benzyl acetate



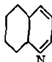
and benzyl benzoate



were next studied and found to act much like papaverin They are metabolized are low in toxicity and have been employed by Macht with excellent results in conditions of excessive peristalsis of smooth muscle

Macht through analyzing the structure of various alkaloids has succeeded in determining the properties of the various groups and through the recognition of the importance of the benzyl group has placed in the hands of the profession a valuable local anesthetic and two general sedatives capable of overcoming undue contraction of smooth muscles

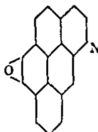
Quinine $C_{20}H_{24}N_2O_2$ Quinolin



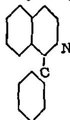
is the structural skeleton of the active principle of quinine and also of nux vomica It is an antiseptic and decreases metabolic rate But it is irritating to the gastric intestinal tract and cannot be used internally It and its isomers have many properties in common with pyridine Quinine is oxymethyl cinchonin with the formula as ascribed by Skraup

(10 mg) papaverin (40) codeine (20) narcotin (30) narceine (10) thebain (10), respectively On combining morphine and narcotin meconates (narcophin) the analgesic power is greater than the arithmetical sum of the effects of its constituents Therefore, true synergism exists in this combination

Later studies followed dealing with the action through the sacral autonomics of several of these alkaloids and other drugs on the ureter An effort was then made to determine the relation of the action of these alkaloids to their chemical structure Morphine belongs to the pyridine phenanthrene group



papaverin and narcotin to the benzyl isoquinolin group,



Morphine was found to increase contraction and tonicity and papaverin to inhibit contraction and to induce relaxation In combinations such as pantopon the benzoyl isoquinolin radicle action predominates This group was therefore investigated, with the result that the relation of the relaxation to the combination of a double nucleus namely the combination of an isoquinolin with a benzyl component was discovered The isoquinolin radicle itself does not produce relaxation The benzyl group therefore was considered responsible for the inhibitory and sedative action of papaverin and narcotin Confirmation was obtained in the action of peronin which is a benzyl morphine Unlike morphine and its other derivatives it produces inhibition An hypothesis was advanced that the inhibitory action of papaverin on the ureter is due to the benzyl constituent and that the stimulating action of morphine is due to the piperidin constituent Extension of the work to the gall bladder yielded confirmatory results but the contraction of the gall bladder produced by morphine and analogous bodies is slight compared with that of the ureter

ketones while tertiary alcohols tend to break down into simpler com pounds The nature of the process is but incompletely understood In the aromatic hydrocarbons the ring is usually left intact oxidation affecting the groups substituting the H atoms of the ring Benzoic acid frequently results combines with glycocoll and is excreted as hippuric acid Oxidation of hydrogen in the beta position sometimes yields beta oxybutyric acid diacetic acid and acetone

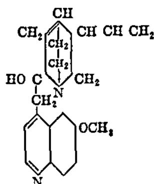
Reduction is effected in the body with more difficulty and instances are relatively rare but chloral is reduced to the corresponding alcohol and excreted as a glycuronate and some nitro bodies are reduced to cor responding amines

Vital Force has been a subject of controversy for long periods With a clearer understanding of various forces the types of forces are disappearing Radiant energy is now classed as a branch of chem ical science and chemical and electrical energy are probably one and the same form of energy In considering as one must the mutual rela tionship of the drug and cell involved in pharmacological action it appears that we have many theories involving facts of very diverse nature In all probability a combination of forces plays a role Barger and Dale ([19]) say The least unsatisfactory view seems to us to be that which regards the existence of stimulant activity as dependent on the processes of some chemical property the distribution and in the main the intensity of activity as due to a physical property

(4) Specific Chemotherapy and Experimental Therapy

The surest and usually the shortest approach to the specific treat ment of any condition is through the experimental reproduction of the disease in animals and through the subsequent application of experi mental therapy Science is built on experimentation Nature s secrets are well shielded Facts must be pried from her through experimenta tion scientific methods constituting a fulcrum But in the human only the most limited experimentation is possible Human life is too valua ble only in desperate conditions are desperate remedies justified But desperate conditions do not permit of recovery as a rule even though the treatment be correct in principle

The value of human life has retarded progress in therapy by blocking the channels through which science ordinarily flows In consequence the physician is limited in his practice to well established usually time honored partially effective non harmful measures His responsibility is heavy and he adheres to the ancient principle primum non nocere Science is not built on isolated observations but on laws established



Quinoline itself has but little antipyretic action in malaria has but little effect on the parasite and in pneumonia has no effect on the fever

At the present time it has not been determined in which radicle the potency of quinine resides It is not thought to be in the quinoline constituent Discussion has been centered about the vinyl (CH CH_2) group in the side chain Hunt ([18]) has shown however that the alteration of the vinyl group in quinine to CH_2CH_3 or to CHOH CH_3 and CHCl CH_3 does not appreciably influence its effect against infusoria

Cupreine has come into some prominence in medicine because of its effect in pneumonia Quinine is methyl cupreine Morgenroth demonstrated that in pneumonia of mice ethyl hydroxy cupreine exercises an effect little short of specific

Influence of Metabolism

Drugs after administration may undergo great alterations Given by mouth changes occur frequently before the tissues are reached In the mouth there is no change as a rule In the stomach the free HCl tends to increase the solubility of basic substances and to break down anilides In the intestine the bile and pancreatic juice cause saponification of fats and esterification also increases the solubility of some organic acids Generally speaking the drugs are changed in such a way that they become less toxic

The chief changes however occur in the blood and tissues Synthesis oxidation and reduction are the three processes best understood In synthesis combinations occur with sulphonic glycuronic and glycocollic acids the end results being most frequently urea and its derivatives glycuronates sulphocyanides and sulphocarbolates These processes are of great importance in the process of detoxification Oxidation affects many drugs in the same manner as it does foodstuffs the end products being CO and H O Partial oxidation facilitates further oxidation The primary alcohols oxidize to aldehydes and acids the secondary to

ketones while tertiary alcohols tend to break down into simpler compounds The nature of the process is but incompletely understood In the aromatic hydrocarbons the ring is usually left intact oxidation affecting the groups substituting the H atoms of the ring Benzoic acid frequently results combines with glycocoll and is excreted as hippuric acid Oxidation of hydrogen in the beta position sometimes yields beta oxybutyric acid diacetic acid and acetone

Reduction is effected in the body with more difficulty and instances are relatively rare but chloral is reduced to the corresponding alcohol and excreted as a glycuronate and some nitro bodies are reduced to corresponding amines

Vital Force has been a subject of controversy for long periods With a clearer understanding of various forces the types of forces are disappearing Radiant energy is now classed as a branch of chemical science and chemical and electrical energy are probably one and the same form of energy In considering as one must the mutual relationship of the drug and cell involved in pharmacological action it appears that we have many theories involving facts of very diverse nature In all probability a combination of forces plays a role Barger and Dale ([10]) say The least unsatisfactory view seems to us to be that which regards the existence of stimulant activity as dependent on the processes of some chemical property the distribution and in the main the intensity of activity as due to a physical property

(4) Specific Chemotherapy and Experimental Therapy

The surest and usually the shortest approach to the specific treatment of any condition is through the experimental reproduction of the disease in animals and through the subsequent application of experimental therapy Science is built on experimentation Nature s secrets are well shielded Facts must be pried from her through experimentation scientific methods constituting a fulcrum But in the human only the most limited experimentation is possible Human life is too valuable only in desperate conditions are desperate remedies justified But desperate conditions do not permit of recovery as a rule even though the treatment be correct in principle

The value of human life has retarded progress in therapy by blocking the channels through which science ordinarily flows In consequence the physician is limited in his practice to well established usually time honored partially effective non harmful measures His responsibility is heavy and he adheres to the ancient principle primum non nocere Science is not built on isolated observations but on laws established

through the study of behavior in repeated experiments under conditions accurately controlled

Although desperate remedies are rarely justified they are frequently needed Once laws governing their action have been established the element of danger can be quantitatively determined and in some instances practically eliminated These laws can only be established through ascertaining the proximity of death which means that death itself must result in certain instances This obviously eliminates human experimentation from consideration and hence we resort to lower animals With the experimental disease all the tools of science are made available the only limitations existing being those of the investigator

Aside from pharmacology experimental therapy centers about three major fields specific chemotherapy immunotherapy, and organotherapy Each of these constitutes an independent branch of science

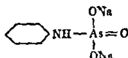
Specific Chemotherapy of Trypanosomiasis

This field of science was created almost entirely through the labors of Paul Ehrlich ([20]) which culminated in the introduction of salvarsan ('606) and of neosalvarsan The character of the work involved the underlying principles covered, and the factors leading to practical results can be best presented by quotations from his preface in his masterpiece Spirilloses and Their Treatment ' A medicinal substance can only act upon the bodily system into which it has been incorporated The object of the researches was to find a distinct curative type and to improve it more and more by means of transformation and substitution Whereas formerly the substances were offered to the medical man by the chemist for testing purposes the conditions could now be reversed and the chemotherapeutist could give the chemist points which lead to the desired recovery of genuine curative substances" In this way he substituted science for chance "It was far more a question of putting the principles of action of medicine on a therapeutic basis the study of what I should like to describe as the therapeutic biology of parasites The success of my work depends upon the conception of chemoceptors obtained in these researches In relation to syphilis he further says, 'It was only by knowledge of the parasite which causes the disease and through the possibility of transferring it to animals that experimental chemotherapeutic work is rendered possible while the specific blood reaction is indispensable in determining the genuine curative action'

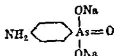
The discovery of trypanosomes ([21]) as the cause of disease in animals surra of camels by Evans (1880) nagana by Bruce dourine by Rouget (1894), and their occurrence in humans by Dutton (1901) and

their etiological relationship to sleeping sickness by Castellani (1903) led to the experimental production of these diseases in animals and to attempts at their cure

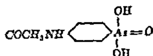
Laveran in 1903 demonstrated that arsenious acid exerted a marked toxicity on trypanosomes, but was incapable of effecting a cure in infected animals Thomas ([22]) of the Liverpool School of Tropical Medicine used atoxyl in experimental trypanosomiasis with good results and sought other forms of arsenic less toxic for the host He considered atoxyl to be the sodium salt of the anilid of meta arsenic acid with the formula



Ehrlich who had previously tried and discarded atoxyl in his studies on trypanosomiasis interested himself in it again subsequent to the report of Thomas and Brienl (°) With the assistance of Bertheim ([2]) he investigated atoxyl chemically being puzzled by certain of its reactions He finally concluded that it was not an anilide of meta arsenic acid but the sodium salt of para amino phenyl arsenic acid

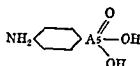


This discovery was of the greatest significance to medical science and constituted the basis of the work which resulted in the development of chemotherapy Thomas made definite progress by establishing the value of atoxyl and in calling attention to the desirability of searching for arsenicals with greater toxicity for parasites and with decreased toxicity for the host Ehrlich on the other hand found the key to greater progress in recognizing the true nature of atoxyl The first conception of it as a fixed anilid admits of no great changes in the molecule whereas its true formula reveals the possibility of the preparation of a whole series of compounds The NH group can be acetylated benzoated can be substituted by halogen or by hydroxyl radicles In this way arsacetin resulted with the formula

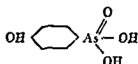


This was found to possess decided advantages over atoxyl being more stable and somewhat less toxic while equally parasititropic It was used clinically in sleeping sickness with fair results

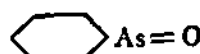
Ehrlich's efforts were next directed to determining the method in which atoxyl acts In vitro it was not strikingly toxic to trypanosomes but after administration serum containing it, it was extremely toxic acting in dilution of 1/120 000 according to Koch Ehrlich conceived the idea that the increase in toxicity after administration was due to reduction of the arsenic, i e that the arsenic became trivalent instead of pentavalent In this connection the following facts were established



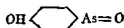
(atoxyl) does not kill in five per cent solution in one hour,



(p oxyphenyl arsenic acid) kills in one to two per cent solution



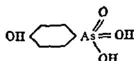
(arsenoxide) kills in 1/100 000 in one hour,



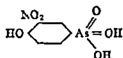
(paroxyphenyl arsenoxide) kills in 1/1 000 000 in one half hour Reduction has resulted in increased toxicity as it has done in many other instances CO being more toxic than CO_2 and HCN than HCNO Ehrlich decided that the toxic body concerned in the death of the parasite was not atoxyl but the reduced form of



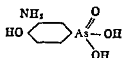
Salvarsan can be made directly from atoxyl It is easier however to start with paroxy phenyl arsenic acid



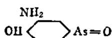
When properly treated with nitrous acid this yields a compound meta nitro paroxy phenyl arsenic acid



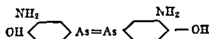
On further reduction this yields meta amido paroxy phenyl arsenic acid



and later meta amido para oxyphenyl arsinic oxide

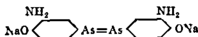


which in turn can be further reduced to dioxy diamido arseno benzol



The reduced form (R — As = As — R) is much less toxic for the host than R — As = O

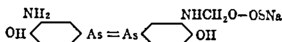
Salvarsan is marketed in vacuum tubes in order to prevent oxidation which readily occurs on exposure and results in great increase in toxicity By the addition of hydrochloric acid it is readily converted into the acid salt NH_2HCl By the addition of NaOH it is neutralized and forms the alkaline base



which is the form in which it is administered It is locally irritating and therefore given now exclusively by the intravenous route

Neosalvarsan or 914 was later introduced by Ehrlich being somewhat less toxic and decidedly less irritating locally It is obtained from salvarsan by the addition of formaldosulphoxylate A sulphoxyl group has the formula SO OH is derived from the sulphoxyl acid (H SOOH) and corresponds to the carboxyl group COOH Salvarsan combines with sodium formaldosulphoxylate (HCOHOSNa) which is

a condensation product of H SO_2 (sulphoxylic or hyposulphurous acid) and formaldehyde (HCOH) Neosalvarsan has the formula



and being readily soluble in water and locally non irritant, may be injected subcutaneously or intramuscularly

The work of Ehrlich constitutes one of the most remarkable achievements of modern medicine It furnished mankind with a useful remedy demonstrated in a most practical way that pharmacological action is dependent upon chemical structure founded chemotherapy, and revealed the methods whereby the creation of specific treatment is made possible He aimed at a cure in one dose for syphilis a "Therapia sterilisans magna In this he did not altogether succeed but he produced the most effective remedy yet found for syphilis and blazed the way for future progress

Ehrlich s Experiments with Trypanosomes—Ehrlich s own animal experiments were conducted on trypanosomes and it was from these studies that he acquired the principles which resulted later in such great discoveries

Mice and rats are readily infected with many species of trypanosomes notably T brucei T evansi T gambiense and T equiperdum Only one who has worked with trypanosomiasis in mice can appreciate the opportunities it offers No more ideal conditions for experimental therapy can be desired A given strain will result in death of the animals with clock like regularity as to time The severity of the infection can be readily ascertained by the number of organisms in the blood as can also the rate of disappearance of the organisms as the result of therapy In addition large numbers of animals can be handled at one time the only facilities needed being jars or cages syringes glass slides and a microscope The technique is simplicity itself

Successful treatment furnishes one of the most spectacular phenomena ever witnessed in the field of therapy A seriously infected animal lying on its side too weak to move and with as many as two or three million wriggling trypanosomes swarming in each cubic millimeter of blood may as the result of a single treatment return within one or two hours to absolute normality so far as can be determined With the disappearance of clinical evidence of disease the organisms disappear entirely from the blood This transformation within an hour from death s door to normality must be seen to be appreciated

The principles established and the laws discovered by Ehrlich are as follows

(1) No organism is affected by a drug unless it is incorporated in the organism or in Ehrlich s own words ' Corpora non agunt nisi fixata which as applied to chemotherapy must be interpreted parasites can only be destroyed by those materials for which they have a certain affinity thanks to which they are anchored by the bacteria In this connection he assumed the presence of chemoceptors

(2) Remedies affect both the host and the parasite only those substances can be employed as medicaments in which organotrophy and parasitotrophy stand in proper relation

(3) By accepting the best remedy available it is possible through modification of its constitution to change its properties and further through experimentation and control it is possible to increase parasitotrophic and decrease organotrophic properties Thus in using atoxyl as the basis the potent part of the molecule was sought Trivalent arsenic was recognized as the essential factor Experimentation proved the possibility of increasing the toxicity of the arsenic of the molecule for the parasite and by working on the benzyl end of the molecule its toxicity for the host was decreased Three objects were attained (a) diminished toxicity (b) increased action on the parasite (3) increased stability of the combination

(4) In chemotherapy experience teaches what types of changes in the molecule are desirable in other words the constitution of a chemical determines its action and the laws governing organotrophic and parasitotrophic properties can be recognized and utilized The investigator therefore must direct the work of the chemist suggesting changes in molecules as they are deemed desirable and not testing drugs made at random by the chemist

(5) Closely allied organisms differ in pathogenicity in the acuteness of the resulting disease and in their resistance to a given therapy while different strains apparently causing the same disease also may differ from each other in the same respects For example T lewisi and T nagana are both trypanosome infections In rats nagana kills quickly and produces a fatal disease which however responds readily to treatment with arsenic whereas T lewisi which occurs naturally in rats does not as a rule prove fatal and is totally resistant to arsenicals In sleeping sickness in Togoland many cures were reported with arsenophenyl glycin whereas the disease as encountered in the Congo was much more resistant

(6) Cures are the more readily obtained the earlier the treatment is instituted

(7) Relapses generally speaking are more difficult to cure than original infections

(8) Treatment unsuccessful in the first instance is usually unsuccessful in repetition

(9) Repeated non curing treatments frequently result in progressively decreased effects on the parasite This condition Ehrlich calls Festigkeit which indicates that the strain has become fast tolerant or resistant to the drug

(10) Repeated non curing treatments with some preparations result in the development of hypersensitiveness on the part of the host to the medicament This was demonstrated by Kline Eckard Ullrich and by Scherschmidt

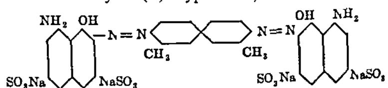
(11) As the ultimate cure by one dose is desirable and best a 'therapia sterilisans magna' should be sought

Ehrlich s work was some years in progress Collaborators working clinically especially in Africa assisted in recognizing and establishing some of these laws so that clinical as well as laboratory experience contributed to the solution of the problems Some of the principles enumerated were recognized independently by other investigators

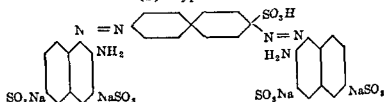
It is interesting to note that among thousands of preparations investigated by Ehrlich and others only four groups of drugs have been found which are strikingly effective in trypanosomiasis These are as follows

(1) Certain arsenicals arsenious acid atoxyl arsacetin arsenophenylglycin salvarsan and neosalvarsan

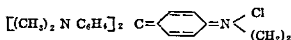
(2) Certain azo dyes (a) trypan blue,



(b) trypan red



(3) Certain triphenyl methane basic dyes, parafuchsin pyronin and methyl violet



(4) Certain antimony preparations—antimony tartrates of potassium and sodium tartar emetic $K(SbO)C_4H_4O_6 + \frac{1}{2}H_2O$ p amino phenyl stibinic acid (corresponding to atoxyl)

$$NH_2\langle\bigcirc\rangle Sb(=O)(OH)_2$$

Aniline antimonyl tartrate

$$Sb\begin{cases} C_4H_4O_6 \\ OHC_6H_7N \end{cases}$$

Triamids of antimony thio glycollate

$$Sb\begin{cases} SCH_2CONH_2 \\ SCH_2CONH_2 \\ SCH_2CONH_2 \end{cases}$$

Sodium antimony thioglycollate

$$Sb\begin{cases} SCH\ COONa \\ SCH_2COO \end{cases}$$

In 1909 before salvarsan was introduced Dr Abel and the writer became interested in chemotherapy and carried out experiments throughout 1910 and 1911 Our interest centered chiefly on the effects of antimonials and arsenicals in trypanosomiasis though as will be seen later we also worked with spirilla and spirochetae The trypanosomes used were (1) T brucei which is responsible for the tsetse fly disease which affects horses mules donkeys and cattle in Africa (2) T evansi (strains from India and Mauritius) which produces diseases of camels and cattle (3) T equiperdum which affects horses producing dourine instances of which are not infrequent in this country The experimental animals employed were rats rabbits and dogs some of which were under observation for a year to eighteen months

Prior to these studies antimony had been tried by others Cushny first suggesting its use Sodium and potassium salts of antimony tartrates (Thomson and Plimmer) p amido phenyl stibinic acid (Breinl and Nierenstein) sodium antimony malate ethyl antimonyl tartrate (Collie Thomson and Cushny) and aniline antimony tartrate (Laveran) of these tartar emetic proved effective but very irritating locally

The substitution of an alkyl radicle as in ethyl antimonyl tartrate resulted *in definite improvement in this respect no local reactions whatever following* its use and cure being effected in seven of the thirteen rats treated

In our work two new compounds of antimony were prepared the triamide of antimony thioglycollate and sodium antimony thioglycollate These chemicals were tested in regard to their efficacy as trypanocidal agents in several series of inoculated rats rabbits and dogs

The difference in the virulence in the diseases produced by these strains of trypanosomes is striking, T brucei and T evansi killed rats regularly in 72 to 84 hours while that of Mauritius and of Dourine were much less virulent a week or even a month elapsing before death in some instances The greatest success was obtained with the triamide of antimony thioglycollate and with sodium antimony thioglycollate

The time elapsing between the date of inoculation and the beginning of treatment is the most important factor in determining the results obtained The longer the period before the institution of treatment the less the degree of success from the point of view of ultimate cure the shorter the period the greater the success These drugs administered 24 hours before inoculation failed to protect but given at the time of the inoculation prevented the development of the disease in every instance With the more virulent trypanosomes after the lapse of 24 hours at which time organisms were beginning to appear in the blood absolute cure was effected but after 48 hours or more permanent cure was infrequent It is possible to drive the organism from the blood so that subinoculations fail By intermittent graded doses it is possible to banish the organism for prolonged periods weeks and months but on the withdrawal of treatment they reappear and the disease rapidly runs its course unabated This can be accomplished with animals which would otherwise die in the course of an hour or two During the time that the blood is free the animal appears perfectly normal in every respect but when treatment is continued the animal after some months finally succumbs to the effect of the antimony

Two problems present namely what becomes of trypanosomes and how do relapses develop?

Examination of the blood subsequent to treatment reveals morphologic changes in the trypanosomes They become slower and tardy in their movements Their bodies become constricted and they take on a more granular appearance such as is commonly seen in them after death and subsequent to the death of the host They undergo involution They finally become immotile the flagella often become detached or adherent

to the centrosome The process is associated with a leucocytosis as a rule and frequently debris from the organisms can be demonstrated in the leucocytes Fever is present in some of the larger animals during the period of blood infection and this may disappear promptly upon their disappearance from the blood

Many investigators have studied the tissues of various organs in the attempt to find a lodging place for the trypanosomes during the period in which the blood is free Emulsions of various organs have been inoculated into animals and controlled by utilizing in others injections of blood from the heart The claim has been made that the liver and bone marrow harbor the organism during this period and that inoculations from these tissues are frequently successful at the time that the inoculations from the heart blood fail Others question this and feel that the further removed from relapse the more frequent the emulsions from organs fail and that only immediately subsequent to treatment and just before relapse is it possible to get positive results from organs at which time the blood is also positive if a sufficient amount is investigated

Ehrlich believes that there exists during this period a true immunity This immunity is specific for the single strain concerned and the immunity reaction may be utilized for the differentiation of strains Subsequently when this immunity wears off generally speaking reinoculation results in infections analogous in every respect to the original infection In this connection Terry has utilized the method to prove that surra of India and surra of Mauritius are not identical He cures surra of India in a mouse and then injects a mixture of surra of Mauritius and surra of India and proves to his satisfaction that the animal develops only surra of Mauritius Provided this is true it is perhaps the most striking instance of drug specificity known to medical science

Relapses are difficult to explain but the following hypotheses have been suggested

(*a*) That on treatment some of the organisms are driven into hiding in some of the internal organs where they are not subjected to the action of the drug Subsequently they reappear in the circulation and cause reinfection

(*b*) That not all trypanosomes are equally susceptible to the influence of drugs and that the more resistant organisms persist This is strongly suggested by studies of the action of drugs on trypanosomes in hanging drop preparations After the vast majority of organisms are killed it is not at all unusual to find isolated trypanosomes still very active

(*c*) That trypanosomes undergo cycles in development and that they are more resistant in some parts of the cycle than in others

Drug Resistance

Tolerance.—During the course of the work with trypan red and arsenicals Ehrlich and his collaborators found that non curative doses which at first sufficed to cause disappearance of the organisms from the blood lost this power subsequently in the same animal Larger doses at first gave some effect but eventually even maximal doses failed to have demonstrable effect on trypanosomes This strain on passage through another animal of the same species remained resistant for many generations This phenomenon Ehrlich called "Festigkeit" It was this resistance which particularly interested him and caused him to continue his work with trypanosomes and it was the study of drug resistance which led to the fundamental conception of chemotherapy responsible ultimately for the introduction of "606" This tolerance on the part of trypanosomes holds only for the particular type of remedy used arsenic antimony, or dye substance but once firmly established it holds for other members of the same group Thus a strain which is resistant to fuchsin is also immune to the related basic dyes but not against azo dyes, arsenicals or antimonials Similarly a strain resistant to arsacetin is also resistant to atoxyl The resistance to atoxyl is easiest obtained next to arsenophenylglycin and finally to tartar emetic

In relation to arsenic resistance a peculiar phenomenon is observed A strain may be made resistant to atoxyl without being resistant to arsenious acid, arsenophenylglycin or antimony In the attempt to make this strain resistant to arsenious acid resistance to antimony or better to tartar emetic develops Another striking peculiarity is the development of a temporary resistance to tartar emetic in producing an arsacetin fast strain without developing resistance to arsenious acid Apparently resistance to arsenious acid is accomplished by resistance to most arsenical derivatives According to Ehrlich's conception the trypanosome has many chemoceptors In relation to arsenic and its acetyl derivatives there exists at least two The formation of one (the arsenoceptor) by atoxyl does not interfere with the acetylceptor which can be brought into play in relation to arsacetin

It is difficult to see why it is easier to obtain resistance to tartar emetic by first establishing tolerance for atoxyl In relation to resistance it is interesting to note that with the antimonials employed by Abel and the writer no resistance developed except perhaps in relation to the donkey In rats many treatments with many passages did not result in the slightest diminution of the effect of the antimonials employed

The Role of the Host.—A drug resistant race produces a disease

similar in every respect to that of the non resistant race The resistance itself remains the same through many generations (thousands) in as many as 100 passages through the same species Passage through another animal usually does not affect the resistance thus a strain atoxyl resistant in the mouse remained unchanged in 46 subsequent passages through rats no treatment with atoxyl having been given in the meantime In transfer to another animal the disease runs its natural course in that animal and the strain regains as a rule its original sensitiveness to the drug in question

In working with the donkey Brienl and Nierenstein encountered resistance to atoxyl which persisted in transferring the strain to the rat In our work we found in two rats which were infected from blood of the donkey under treatment with antimony a temporary resistance to antimony Unquestionably the resistance to the drug is most marked in the animal in which the resistance is established but a lesser degree of resistance is sometimes encountered in passage to a new species Resistance is a property of the strain but is most marked in the species in which it was created

Naturally in relation to arsenic tolerance the arsenic eaters the mountaineers of Styria come to mind Whether or not heredity plays a role in this has never been determined By some the increased tolerance is ascribed to lessened absorption by others to increased excretion That it exerts a decreased effect on the gastrointestinal mucosa has however been definitely determined

Specific Chemotherapy of Spirilla

Hata ([24]) working in Ehrlich s laboratories carried on work on spirilla utilizing the same drugs that Ehrlich used in his work on trypanosomes His investigations dealt with the spirilla of relapsing fever of chicken spirillosis and of syphilis

Spirilla of Relapsing Fever—The effect of each chemical was first studied in the test tube the drug dissolved in water or alcohol being added to a blood containing spirilla mixture diluted with physiological salt solution or isotonic sugar solution to a constant quantity Usually a dilution of the blood of thirty to forty fold was attained The motility of the spirillae was investigated at the end of one hour immotility being interpreted as death

The animal experiments were carried out with mice and rats with an attenuated virus but with equal infections so far as possible in all cases i e one in which the organism could be found in the blood of the animal on the following day and in about equal numbers this necessitating con

stantly greater dilution for the same quantity injected, since virulence increases with constant passage The amount of blood necessary for this varied with different strains, and with different conditions Nevertheless it was possible to obtain a fairly constant infection The disease as its name indicates presents frequent relapses provided the animal does not die in the first attack Animals were grouped in series according to the mortality of the untreated condition inasmuch as continuous passage through one specifies invariably results in increased virulence Chemicals were administered on the day after inoculations and the blood studied microscopically thereafter for a period of 60 days since relapses occur as late as 50 days

In some instances test tube and animal experiments give similar results but not invariably Obviously the animal experiments yield the truer criterion for practical results The most striking results were obtained with arsenicals The three arsenicals atoxyl arsacetin and arsenophenylglycin were practically inert against the spirilla Arsenophenol was itself more effective while its derivative dioxy diamido arseno benzol both as acid and alkaline salt was wonderfully effective The effect in the test tube is but slight solutions of 1/10 000 being necessary to kill the spirilla Organisms subjected to 1/10 000 solution of the drug if still motile cause the disease but with a modified course With dilution of 1/100 000 the disease develops immediately Permanent cure however could be effected on the first day following inoculation by doses well below the danger line

Hata determined the toxicity of dioxy diamido arsenobenzol for various animals with the following result

Animal	*Application*	*Dose tolerated*
Mouse	subcutaneously	1 300 per 20 gms *)
	intravenously	1 300 20
Rat	subcutaneously	0 [illegible] gram per kg
Hen	intramuscularly	0 25
	intravenously	0 08
Rabbit	subcutaneously	0 1
	intravenously	0 15

* 1 c c of 1/300 soln

Animals vary somewhat in susceptibility to both the disease and the drug But by taking a series of animals it is possible to arrive at a fair average in relation to both The important desideratum to determine is the relation of the curative dose to the dose tolerated Thus for mice Hata found the following in relation to permanent cure

Dose	*One Treatment*	*Two Treatments*	*Three Treatments*
1 600	100 per cent		
1 700	100		
1 800	100		
1 1000	75	100 per cent	
1 1500	18	75	100 per cent.
1 000	16	66	100
1 3000	0	0	33

This result is important as indicating the increase in effectiveness in repetition of the treatment Better results were not obtained with more than three treatments

The dose curative as related to the dose tolerated was represented by $\left(\frac{C}{T}\right)$ The following results were obtained with single and repeated injections

With single injections 300/800 or 1/2 7
With two injections 300/1000 or 1/3 3
With three injections 300/1500 2000 or 1/5 to 1/7

He also found that double the curative dose did not entirely protect animals which were inoculated 24 hours subsequently although the course of the disease was modified Rats he found tolerated relatively large doses and the $\frac{C}{T}$ was more constant (0 06 to 0 08 gms per kg) completely sterilized and was well tolerated in all instances

As the result of his work it was evident that relapsing fever in mice and rats could be readily cured by single doses of these arsenicals without untoward effects of any kind

Experiments with Spirillosis of Fowls—Spirillosis of chickens is easily cured by arsenicals Uhlenhuth and Gross demonstrated the effectiveness of atoxyl and Uhlenhuth and Manteufel that of atoxyl acid mercury The blood of canaries on the third day was diluted 15 to 20 times with salt solution so that it showed about 20 spirilla to the field and of this mixture 0 5 c c was injected intramuscularly In Hata s work treatment started on the second day at which time the blood was but lightly infected Untreated animals showed a mortality of thirty three per cent The drugs tested were injected into the pectoral muscles and the blood of the animal was examined subsequently at frequent intervals Many arsenicals gave good results the best however being obtained with diamino dioxy arsenobenzol A curative dose afforded considerable immunity The relative value of various arsenicals is indicated in the following table compiled by Hata

Atoxyl	0 03 / 0 06	C/T = ½
Arsacetin	0 03 / 0 1	1/3 3
Arsenophenylglycin	0 12/0 4	1/3 3
Arsenylic acid Hg	0 04/0 1	1/2 5
Dioxydiamido arsenobenzol	0 0035/0 2	1/58
Amido phenol arsenoxyd	0 0015/0 03	1/20

Specific Chemotherapy of Spirochetes (Syphilis)

The brilliant success attending the use of arsenicals in experimental trypanosomiasis and spirillosis attracted to them widespread attention which resulted in their being tried in syphilis Atoxyl was studied in relation to syphilis in apes by Metchnikoff ([25]) Salmon and Uhlenhuth and his collaborators and in syphilitic keratitis of rabbits by Uhlenhuth ([26]) and Levaditi ([7]) The results were most encouraging In the meantime clinical studies with atoxyl were started at the suggestion of Salmon by Lesser ([28]) Lasser Qwanga and von Zeissl all reports indicating that its effect was considerable Other arsenicals were tried arsacetin by Neisser ([29]), arsenophenylglycin by Alt and cacodylates by Murphy in this country

Ehrlich and Hata applied themselves to the investigation of syphilis using the same methods which had proved so successful in their other chemotherapeutic studies The work was carried out on rabbits in which two forms of syphilitic diseases can be produced namely keratitis and syphilis of the scrotum The efficacy of the treatment was determined by noting the effects on the lesions and was further controlled through Wassermann studies

Syphilis of the scrotum was first produced in rabbits by Osiola and later by Truffi ([30]) A fragment of cornea from experimental luetic keratitis is transplanted under the skin of the scrotum In approximately two weeks a small patch of infiltration appears which increases in size to that of a bean then breaks down becomes encrusted ulcerates and presents an infiltrated raised margin In the untreated animal the chancre persists for as long as four or five months at times but it is difficult to obtain a uniform disease such as one obtains in trypanosomiasis The Wassermann becomes positive and remains so The condition is one admirably adapted to chemotherapeutic studies the Wassermann reaction provided care is exercised in the selection of the inoculated animals furnishing an excellent and reliable means of control for the general condition while the local lesion the chancre lends itself to ordinary clinical investigations and to the determination of the presence or absence of treponema

Selected infected animals were subjected to intravenous treatment in varying dosage with the different arsenicals With diamido dioxy arsenobenzol Hata found that *the spirilla can be destroyed absolutely and immediately by a single injection* and that *no relapses occur* and that the local lesion subsequently dries up rapidly and disappears This solved from an experimental viewpoint at least the treatment of syphilis From an experimental basis the therapia sterilisans magna was attained

The Introduction of Salvarsan into Practice —The next investigation concerned the clinical value of salvarsan as the preparation was now called Ehrlich determined to subject it to critical tests to prove or disprove its value before introducing it into general use He says many thousands of patients must be treated before the preparation should be available for general introduction For even if a preparation has been tested in the most careful way by means of experiments on animals and has been recognized as good this naturally does not prove that it is also *applicable for human beings Idiosyncrasy to drugs plays considerable* role in relation to human therapy but is apparently a negligible factor in animals Salvarsan was therefore subjected to crucial tests in some of the leading clinics its value established and its dangers ascertained prior to its being offered to the profession

Special commendation must be accorded Ehrlich not only for his brilliant work in chemotherapy but also for the sound clinical judgment exhibited in the method adopted in introducing salvarsan into practice It was first used in selected cases in the best clinics under the closest supervision its effects being carefully followed Later it was used in types showing complications and its contraindications and untoward manifestations determined Eventually satisfactory methods of administration and dosage were determined so that on coming into general use excellent results were obtained from the first and accidents were extremely infrequent

These studies have the greatest significance in medicine They have not only yielded efficacious specific treatment for syphilis relapsing fever and sleeping sickness but have revealed the possibilities of actually creating specifics for disease and have demonstrated beyond question the advisability of determining further the relation of pharmacological action to chemical constitution

Specific Chemotherapy in Protozoal and Bacterial Diseases Contrasted

It is in the field of protozoan infection that chemotherapy has wrought such brilliant results The plasmodium of malaria the

trypanosome of sleeping sickness the treponema of syphilis the spirilla of relapsing fever and of chicken spirillosis all yield to specifics But in infectious diseases only a beginning has been made there being but one or two drugs in the entire pharmacopeia which may be said to exercise a specific effect on infectious diseases (Vide infra)

The explanation for the relative failure of drugs in infectious diseases is not apparent Syphilis offers the best opportunity of revealing the secret as it is so closely allied to infectious diseases For many years syphilis was considered an infectious disease due to Lustgarten's bacillus The lesion produced is an infectious granuloma similar to that seen in tuberculosis and leprosy Not until 1905 was the spirocheta pallidum discovered as its cause by Schaudinn and Hoffmann

Later this organism was reclassified and named treponema pallidum The treponema are very closely related to spirilla which in turn are closely related to bacteria

It is difficult to determine where protozoa end and where bacteria begin The animal and vegetable kingdom merge in such a way that doubt often arises as to which is concerned Reliable criteria are wanting A comparative study of the borderline infections is of the greatest importance

Immunity reactions interest the bacteriologist and serologist The work on trypanosomes furnished the laws of chemotherapy which eventually lead to a cure for syphilis The treponema which is surpassed in versatility only by the B typhosis has already been brought under control The writer is sanguine enough to expect similar results in infectious diseases when the combination of genius perseverance chemistry biology and organizing capacity of an Ehrlich is brought to bear on the problem

(5) Infection and Antiseptics

The discovery by Pasteur of microorganisms as the cause of disease has revolutionized many of the principles and much of the practice of therapy Immunotherapy however is sharply defined from pharmacology It deals at present largely with infection and with specific immunity reactions These undoubtedly are physiochemical in origin but from this point of view are as yet but little understood Because of the definite line of cleavage immunity treatment will not be discussed here

Pharmacology deals with bacteria borne diseases at but a few points the more important being (1) in the treatment of pneumonia (2) in the treatment of rheumatism (3) in the treatment of diseases of the

genito urinary tract and (4) in antiseptic surgery particularly in the use of the Carrel Dakin treatment

(1) *Pneumonia* —Morgenroth and Halberstaedter demonstrated the efficacy of ethylhydroxy cuprein against the pneumococcus In experimental pneumonia its effect is little short of specific and much greater than that of quinine All strains of pneumococci are inhibited by it in vitro in dilution of 1/100 000 Some promising results have been secured in practice but its application is limited owing to a tendency to produce blindness and on the whole its use so far has not been satisfactory

(2) *Rheumatism* —Much discussion has centered about the question of specificity of action of salicylates in rheumatism Salicylates unquestionably lower the fever and remove the pain in the majority of cases of acute rheumatic fever On the other hand the incidence of endocarditis is not diminished On the latter account it has been argued that salicylates have no specific action but so far as their effect on fever and pain is concerned they have a definite action and in many instances they shorten the course of the attack

(3) *Diseases of the Genito urinary Tract* —Certain chemicals manifest antiseptic action against local infection in the body Thus hexamethylamine in acid urine unquestionably affects the colon bacillus and exerts a curative action in pyelitis and cystitis Other chemicals notably argyrol protargol and certain dyes influence the course of gonorrhea These however *do not belong in the same category with salvarsan and syphilis*

(4) *Antiseptic Surgery* —Following the work of Pasteur and the adoption of the germ theory Lister applied antiseptic principles to surgery Aseptic surgery in reality a form of preventive medicine proved so effective that upon it was laid the greater stress antisepsis in consequence not receiving the attention it actually merited

But with the advent of war came the need for antiseptic surgery For reasons quite obvious asepsis was inapplicable Lister s doctrine and methods were tried but with disappointing results which at first were ascribed to technical inadequacies but later to incorrect principles In fact eminent authorities insisted that sterilization of war wounds was impossible and that the treatment of suppurating wounds by means of antiseptics is illusory and that belief in its efficacy is founded upon false reasoning Lister s clinical observations and experiences were forgotten replaced by theories and experiments in vitro which failed to approach the actual conditions confronted

The problem was attacked by Carrel ([31]) and Dakin ([32]) on simple and logical grounds to wit the utilization of a substance non irritating

to the tissues and of sufficient bactericidal power to kill all microbes of all varieties present in the wound, for in the beginning at least surgical infection is local in character Dakin set about finding such a substance and Carrel devoted himself to finding the most effective manner of applying it

The problem was chemotherapeutic in nature Methods such as were employed by Ehrlich were adopted Various antiseptics were tried until the most desirable were determined and these were then modified to best meet the conditions

The Chemotherapy of the Newer Antiseptics

The germicidal action of free chlorine and the hypochlorites is well known In medicine this action has been obtained through the use of chlorine water chlorinated lime Labarraque s solution (solution of chlorinated soda) and Javelle water (solution of chlorinated potash)

Hypochlorite solutions are relatively permanent provided they are alkaline but the degree of alkalinity encountered in Labarraque s solution for instance is destructive to the tissues and skin as well as to bacteria The problem chemically consisted of retaining the bactericidal while deleting or minimizing the tissue destroying properties of the preparation

Tissue destruction was found to be dependent to a large extent on the alkalinity Therefore the usual solution of chlorinated soda made from chlorinated lime and monohydrated sodium carbonate was neutralized with boric acid to the degree of alkalinity determined by experiment to be least irritating to the tissues This was found to be at a point where on adding powdered phenolphthalein no color reaction occurred while the addition of one per cent alcoholic phenolphthalein solution still resulted in a red flash the color quickly fading Such a solution can be used without marked irritation to well vascularized tissues The skin however proves an exception which necessitates the use of petrolatum as a protective agent

Raschig had already shown that the addition of ammonia to hypochlorite solution resulted in the formation of chloramines Dakin ascribed the antiseptic power of resulting compounds to the NCl grouping since "The parent substances from which these chloramines are prepared whether substituted or containing chlorine attached to carbon show no such action ' A series of substances containing the NCl grouping with sulphur benzine naphthalene and other radicles were investigated with the following important conclusions

"(1) Almost all the substances examined containing the NCl group possess very strong germicidal action

'(2) The presence in the molecule of more than one NCl group does not confer any marked increase in germicidal power

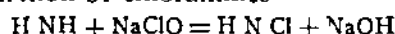
(3) The germicidal action of many chloramine compounds is molecule for molecule greater than that of sodium hypochlorite

(4) The chloramine derivatives of naphthaline and other di cyclic compounds or the sulphochloramide type closely resemble the sulphur aromatic chloramines in germicidal action

(5) Bromamines are less effective as germicides

(6) Derivatives of proteins prepared by the action of sodium hypo chlorite and containing NCl groups are strongly germicidal Blood serum inhibits their germicidal action to much the same extent as it does with sodium hypochlorites and the aromatic chloramines

Mode of Action of Hypochlorites—Dakin has duly considered the mode of action of hypochlorites and offers the following explanation When the hypochlorite solution comes into contact with protein a reaction occurs analogous to the interaction between ammonia and hypochlorites resulting in the formation of chloramines

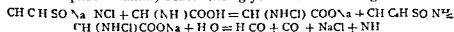


$$H\ NH + NaClO = H\ N\ Cl + NaOH$$

The bactericidal effect is chemical in nature due to such a reaction occurring in the protein of the organism itself or in the medium in which the organism is suspended in either instance the resulting chloramine being responsible for the death of the microbe In this reaction Cl is substituted for the H of the amino group (NH) the Cl uniting directly to the N with the formation of chloramine In other words the capacity of hypochlorites to attack proteins and to form compounds with them in which the halogen is directly attached to the nitrogen is responsible for their bactericidal effect

The destructive action of hypochlorites on skin and tissue is associated with their soda content Their action on living tissues according to Guillaumir and Vienne is modified by the concentration present of other salts a process known to the tanners as pickling Dakin corrected the excess alkalinity but whatever the explanation the fact remains that living tissues evidence marked resistance to the destructive action of Dakin s solution

Mode of Action of Chloramines—Chloramines kill organisms more readily or at a lower molecular concentration than corresponding hypo chlorites from which it may be argued that the compound as a whole exercises some toxicity They react with amino acids peptones and proteins in the same way as hypochlorites thus chloramine T (p toluene sodium sulphochloramid) reacts with glycin in the following manner



$$CH\ C\ H\ SO\ Na\ \ NCl + CH\ (NH\ )COOH = CH\ (NHCl)\ COONa + CH\ C_6H\ SO\ NH_2$$
$$CH\ (NHCl)COONa + H\ O = H\ CO + CO\ + NaCl + NH$$

Peptones and proteins probably react in a manner similar to amino acids but more slowly It appears that chloramines can act as chlorinating agents upon important constituents of living cells, and this may play an important role in their antiseptic properties

As a result of these facts Dakin drew the following tentative conclusions

(1) The fact that proteins contain N in a form capable of attracting Cl from chloramines, is probably a factor in the germicidal action of chloramines

(2) The superior germicidal action of chloramines over hypochlorites is due to special toxic action of the chloramine molecules, or 'possibly to selective chlorination of particular cell constituents'

Carrel s problem cannot be better summed up than has been done by himself Speaking of his method he says The method therefore is based upon the employment rigorously controlled by the microscope of an approved agent under conditions of contact of concentration and of duration established by direct experiment upon infected wounds'

In order to determine its effectiveness an antiseptic must be considered from the following points of view its capacity of irritating tissues, its toxicity its solubility its power of penetrating the tissues and of being absorbed by them and the manner in which it reacts with product and other constituents of the tissues

Each of these factors received special consideration and was made the subject of experimentation Because of their important role in the action of antiseptics proteins were considered in all their work microorganisms being suspended in blood serum instead of water while determining the antiseptic properties of drugs The importance of this is indicated in the following table compiled by Carrel and Dehelly from experiments of Dufresnes on the action of antiseptics on bacteria

Antiseptics	*Without blood serum*	*With blood serum*
Acid carbolic	1 250 —	1 50 —
	1 500 +	1 100 +
Acid salicylic	1 2500 —	1 100 —
	1 5 000 +	1 250 +
Hydrogen peroxide	1 3 500 —	1 1 700 —
	1 8 000 +	1 2 000 +
Iodine	1 100 000 —	1 1 000 —
	1 10 000 000 +	1 2 500 +
Bichloride of mercury	1 5 000 000 —	1 25 000 —
	1 10 000 000 +	1 50 000 +
Nitrate of silver	1 1 000 000 —	1 10 000 —
	1 10 000 000 +	1 25 000 +
Hypochlorite of soda	1 500 000 —	1 1 500 —
	1 1 000 000 +	1 2 000 +

The sign (+) indicates that the culture is positive and the sign (—) that it remained sterile

The power of penetration was determined by immersion in antiseptic solution of small blocks of infected tissues followed by incubation and subsequent cultures In this manner it was found that hydrogen per oxide for instance failed to sterilize blocks of infected liver when cubes larger than one millimeter were employed B welchii being the infecting organism

The effect on tissues was ascertained in the following manner Dakin s solution Eau de Javel and Labarraque s solution all of equal strengths (0 5%) were placed in containers To each was added a frag ment of skin from a stillborn babe At the end of two hours the frag ments in Javel s and Labarraque s solutions were greatly swollen and the epidermis readily detachable subsequently they became transparent and in ten to twelve hours were completely dissociated The tissue in the Dakin s solution after twenty four hours was in a condition similar to that existing in the other solutions after two hours

The antiseptic solutions were next studied in infected wounds them selves When hypochlorite of soda is applied to a wound in such a manner that its degree of concentration remains constant and the dura tion of the application is prolonged the microbes disappear It was determined that this result was not due to spontaneous sterilization to mechanical washing away by the instilled liquid or to alkalinity of the solutions Toxicity was determined by subcutaneous and intravenous injections into animals

The action of the antiseptics on living wounded and healthy tissue was next investigated Dakin s solution possesses a concentration which allows one to make use of the differences of resistance presented on the one hand by microbes free anatomical elements and necrosed tissue and on the other hand normal tissue equipped with a circulation It destroys the first and does not damage the second The factors con sidered in their work in this connection were the condition of the wound the measurement of wounds the cicatrization of infected wounds and the cicatrization of aseptic wounds the influence of the drug being deter mined in each instance

The following preparations after intensive study in war surgery have proved of value as local antiseptics surgical solution of chlorinated soda (Carrel Dakin) chloramine T and dichloramine T

The Carrel Dakin solution in concentrations up to 0 4 or 0 5 per cent is applied by practically continuous irrigation according to methods developed by Carrel which however are too technical to be discussed in this connection Chloramine T sodium paratoluenesulphochloramide in one half per cent aqueous solution is used in the same way It has the advantage of greater solubility convenience of preparation and less local

irritation but lacks the solvent action of the hypochlorites It can be prepared up to eight per cent by solution in chlorcosone or chlorinated paraffin oil Dichloramine T or paratoluenesulphondichloramide is but slightly soluble in water and hence is used exclusively in oil (chlorinated eucalyptus oil or chlorcosone) It is more irritant and also more solvent than chloramine T

Surgical Experience with These Antiseptics

Abundant proof has accrued as to the value of these newer antiseptics Opposed by some, enthusiastically received by others they have been weighed in the balance in war surgery and have not been found wanting Like all other remedies they have their indications and contraindications

In all cases general surgical principles should first be applied In fact some surgeons still believe that the debrisement operation mechanical cleansing and physiological rest are all that are necessary But of those who have tried debrisement alone, and Carrel Dakin s treatment alone and the combination of the two the majority recognize great virtues in these antiseptics *

The chief value of these antiseptics is found in the treatment of infected wounds where the infection is near the wound surface or superficial in character The exudate present appears to enhance somewhat the antiseptic action and to prove a source of protection against tissue destruction on the part of the solution Thus superficial abcesses infected burns infected abdominal wall wounds and amputation stumps where suppuration already exists respond particularly well Sterilization of the ulcer with Dakin s solution immediately increases the chances for " takes " in skin grafts

On the other hand clinical experience has proved that in fresh uninfected wounds and in the presence of great cicatrization Dakin s solution is of but little value and harmful at times In the former Dakin s solution results in the destruction of tissues especially to those poorly vascularized such as cartilage and tendons Nerves on the other hand are but little affected In deeply infected markedly cicatrized or stratified wounds the treatment usually fails utterly

In applying the treatment certain cardinal considerations must be borne in mind namely contact of the solution with every part of the wound mechanical cleansing of the wound with the removal of all foreign bodies the use only of solutions properly prepared and of proper strength and finally absolute adherence to the technique described until

* These statements emanate from the large experience of my surgical colleague Dr J F Corbett who has utilized these antiseptics extensively in war surgery and in the wards of the university hospital

such time as experimental and clinical proof is furnished of the superiority of modifications Only by strict observance of the e directions can the best results be obtained

(6) The Role Played by Glands of Internal Secretion

Metabolism —Eternal as the everlasting hills metabolism goes on the basis of life and all its phenomena While men may come and men may go like Tennyson s brook it goes on forever Species are cast in variou molds generations appear and di appear youth is followed by age yet through it all running along on predetermined lines goes metabolism Where there is life there is chemical reaction and regulating this are the endocrine glands the glands of internal secretion

Protoplasm from the physician s point of view is not matter The cell is the seat of vitality of chemical exchange of growth of function and of life The assimilation of nutriment growth reproduction of kind inflammation degeneration regeneration exercise of function motion and emotion are all matters of chemistry Species genus and time of life are accidents determined by heredity while size weight and sometimes appearance are matters of metabolism which in the individual is controlled by the internal secretions and al o by the nervous system

Physiological alchemy held sway for centuries and introduced many fundamental ideas Exact sciences physiology and physical chemistry are rapidly replacing it bringing light into darkness

The basis on which the science of nutrition rests was laid in 1780 by Lavoisier Lusk ([33]) says of him He was the first to apply the balance and thermometer to the investigation of the phenomena of life and he declared La vie est une fonction chimique He established the true character of the dephlogisticated air of Priestley and through researches on animal heat and on respiration established the relationship of oxygen to bodily functions He quantitatively determined in man the oxygen used per hour the influence of temperature on the quantity u ed the relation of oxygen to digestion and to exercise thus establishing the relation of oxygen absorbed and CO_2 excreted to food work and temperature

Liebig ([34]) became interested in nutrition and studied biology along chemical lines Voit inspired by his work devoted himself to problems of nutrition but particularly to the role played by nitrogen in protein metabolism He calculated the nitrogen content of food determined its excretion in the urine and showed the relationship of urea output to nitrogen intake He suggested to Pettenkoffer ([3]) the need of an apparatus by which the total carbon excretion might be measured a problem

which they undertook jointly The respiration apparatus was completed in 1862 Voit next computed from the substances oxidized in the body the quantity of heat which should have arisen from the destruction of these substances ' Thus was established indirect calorimetry

Rubner in 1894 working in Voit s laboratory made accurate determination through calorimetric methods of the heat value of urea and of dry urinary solids through which were established biological standards for the caloric values of proteins carbohydrates and fats In 1894 he *built the first successful respiration calorimeter which actually measured* heat production in the dog and in so doing established direct calorimetry

Atwater while in Germany was associated with Voit and Rubner In 1877 he investigated the dietary requirement In 1894 through the assistance of the American government he and Rosa started the construction of a respiration calorimeter for man which was completed in 1897

Through the labors of Lusk Benedict and Dubois ([80]) calorimetry has been made applicable to clinical medicine and practical therapy Indirect calorimetry is coming into general use in the larger clinics For comparative purposes a normal control is always essential This for clinical studies is found in the rate of basal metabolism which is expressed in calories per hour per square meter of body surface The variation from the normal average is expressed in terms of percentage above and below normal

In this manner developed the science of nutrition whereby is revealed the function value and fate of food Through gas analysis determinations of heat production and analysis of excreta the possibility was revealed of determining quantitatively the role played by various foods such as proteins carbohydrates and fats in metabolism and their relationship to heat and energy production to growth and to the processes of building up and repairing of tissues With increase in the knowledge of metabolism of physiological chemistry and of medicine in general the relation of disturbances of metabolism to disease became manifest Detailed studies of these disturbances is shedding much light on both the processes of normal metabolism and that of disease

In metabolic studies attention centered in the mechanisms involved in digestion storage and assimilation of foods in their fate and function under varying conditions and in the factors affecting metabolic processes generally such as *oxidation, cleavage, deamidization* reduction and synthesis

Nutrition and Food Values

In the space allotted it is impossible to attempt more than an outline in a general way of the more important phases of nutrition the role

played by the glands of internal secretion and the use of glands or their products in organotherapy

Foods are utilized by the body as (a) material for construction of body substance (b) to make good the losses incurred in the wear and tear of life i e maintenance (c) to supply energy for life s activities and (d) to supply heat The foods required are carbon hydrogen nitrogen oxygen sulphur phosphorus chlorine iron salts and water Some of them must be prepared since higher organisms have not the same capacity as the lower of building up their own food from simple chemical compounds The carbon and hydrogen produce energy through oxidation nitrogen is utilized for repair of structures containing nitrogen and secondarily for energy oxygen is needed for oxidation of carbon and hydrogen and is the chief source of energy sulphur is necessary for growth and repair of structure containing sulphur phosphorus for growth and repair of structures containing phosphorus iron for hemoglobin salts for osmotic pressure and water for facilitating solution and for carrying off waste products in excretion The nitrogen and carbon must be in forms as complex as amino acids and the sugars respectively The classes of foodstuffs are ordinarily carbohydrates proteins and fats the caloric values of which have been accurately determined But calories do not always suffice these may be supplied in abundant quantities without maintenance or growth

It is just at this point that recent advances have been made In addition to caloric values there are other factors known as accessory factors These are of two kinds (a) originating from without bausteine and vitamines (b) arising from within hormones or internal secretions

Bausteine or Building Stones—Proteins from different sources differ chemically and biologically Newer knowledge of the structure of these highly complex nitrogenous compounds makes possible a new conception of protein metabolism The nitrogen must be in the form of a molecule at least as complex as an amino acid before it can be utilized in the body Such units constitute building stones or bausteine The work of Osborne and Mendel ([27]) and of McCollum ([1]) in this country and of Abderhalden ([2]) in Germany introduces a new conception of nutrition and also a broader conception of the function of the cell in its capacity to synthesize

Proteins are broken down in digestion into amino acids These are absorbed circulate as building stones and are utilized by the cell in the building up of new protein For maintenance certain amino acids are necessary for growth still others are needed In so far as a protein possesses in its molecule the building stone needed just so far can it be

utilized for maintenance or growth For example if only proteins deficient in cystin (a sulphur containing amino acid) are furnished the body the production of new cystin containing bodies will be difficult and limited by the supply in the food ingested Through feeding artificial food mixtures to mice the importance of certain bausteine have been demonstrated tryptophane for maintenance and glycin and lysin for growth For maintenance the addition of tryptophane is necessary to zein carbohydrate and fat diet and also to completely hydrolyzed (enzymatic) proteins For growth of mice milk must be added to mixtures of pure caseinogen fats carbohydrates and salts and lysin to certain other food mixtures The body can however synthesize glycocoll

Similar requisites probably exist in the field of lipoids Thus cod liver oil so long utilized in nutritional diseases of childhood is shown to facilitate growth in mice in artificial food mixtures when lard fails This is another instance of sound empiricism which is now being rationalized

Vitamines.—For normal metabolism vitamines are necessary Little is known of their character or of their mechanism of action In their absence diseases appear Reintroduced to the diet after prolonged absence they sometimes result in cure Lack of fresh vegetables and fruit juices may result in scurvy lack of rice polishings in beriberi while absence of eggs meat and milk in the diet is responsible for pellagra These are known as deficiency diseases and their treatment consists of the addition of appropriate foods to the dietary

Funk (40) who first recognized the existence and importance of vitamines, has attempted their isolation To the vitamine of rice polishings he has ascribed the formula $C_{6}H_{-1}O_{9}N_{4}$ and believes it to be a tetrabasic acid But inasmuch as its formula closely resembles that of nicotinic acid (41) (an inert substance from this point of view) further work is necessary Hopkins (42) feels that the true vitamine is still unknown It belongs to the "water soluble A" class of McCollum

Hormones Internal Secretion.—The work of Starling and Bayliss (43) resulting in the recognition of hormones or internal secretions opened up a new chapter of physiology and revealed the existence of another factor in metabolism which is of the greatest importance to medicine The endocrine glands manufacture substances which act as catalysts and markedly affect metabolism Under or over production of them results in the development of diseases of metabolism thus the absence of thyroxin leads to myxedema of the secretion of pancreas (islets of Langerhans) to diabetes, of tethelin to infantilism of the extract of the posterior lobe and pars intermedia of the pituitary to diabetes insipidus,

of the parathyroids to tetany and of some secretion of the adrenals to Addison s disease On the other hand excess of thyroxin leads to exophthalmic goitre and of tethelin to gigantism or acromegaly

These secretions are chemical entities one of them thyroxin having already been synthesized and used therapeutically Future therapy will probably use synthetic drugs to replace these internal secretions in the diseases of metabolism in which they are deficient

In relation to metabolism attention should be called to the specific dynamic action of protein In studies of basal metabolism it has been found that proteins stimulate the rate of metabolism more than carbo hydrates Some of the amino-acids for instance glycin and alanin exhibit this property It is supposed to be due to the direct timu lating action of some of the intermediary acids such as lactic and peruvic

Little is known concerning the effect of drugs on metabolism but since the synthesis of thyroxin has already been accomplished it would appear that the day of drug control of metabolism is at hand The influence of caffeine and strychnine has been determined by Edsall and Means (") and Higgins and Means (*) and of adrenalin by Sandif ord Opium is said to slow the rate of metabolism The effects of these drugs on metabolism are in all probability due to their effects on the neuro muscular system whereby acceleration on the one hand and inhibition on the other occur Cacodylate of sodium has been utilized clinically to control the increased rate of metabolism in exophthalmic goitre arsenic and phosphorus in therapeutic doses are both said to check oxidation and to favor nutrition in growth

Gro th

A new science of growth is in the making Life is a sequence embryonic life birth infancy childhood adolescence maturity and senility follow each other unless death intervenes Growth characterizes the young According to Lee it consists of only three processes multiplication of cells enlargement of cells and deposition of intercel lular substance Great variations from the mean are uncommon and until recent years have not been subject to explanation But investiga tion in the field of growth nutrition and hormone actions is doing much to elucidate this subject

Growth is a function of the cell Two or perhaps three fundamental factors are concerned namely growth impulse nutrition and acces ory factors such as hormones and vitamines The first we do not understand it is life itself Nutrition is controlled by laws of physiology of chem istry and physics The importance of the accessory factors are just

beginning to be recognized Growth is regulated for each species the same food in the same amounts fed to different species resulting in different rates of growth

Metabolism or nutrition in the young organism differs in some respects from that of adult life Additional processes are at work involved in changes in character of tissue such as ossification of bone and union of epiphyses But the chief difference lies in growth or the creation of new tissues which involves the building up of new proteins *The ordinary foodstuffs play the same role as in adults* Maintenance can be procured in mice on the same artificial food mixtures utilized in the nutrition experiments for growth but the histeine tryptophane glycin and lysin are absolute requisites for growth The addition of small quantities of lactalbumen and of edestin to zein fed to mice increases growth out of all proportion to the amount added

The glands of internal secretion play a great role in growth as well as in nutrition The addition of thyroid extract to the food of the cretin revolutionizes not only his metabolism but his growth and with it his appearance his physical and mental development According to Brailsford Robertson ([46]) tethelin a substance obtained from the anterior lobe of the pituitary plays the leading part in the control of growth The pituitary came under suspicion naturally in this connection owing to the intimate association of gigantism infantilism acromegaly and obesity *to tumors of the hypophysis Other glands such as the thymus* and the gonads unquestionably are concerned also to some extent

Energetics

Energy is the capacity for doing work Energy characterizes life The ultimate source of energy is the sun the immediate source for the living body is its nutriment Various classes of food have different food values but equal heat values do not of necessity have equal free energy values for energy is of two kinds bound and free only the latter being *available for actual work The total energy is constant* the bound tends to a maximum therefore the free tends to diminish Some foods are more easily metabolized than others and their energy is quickly available Free energy the ability to do is the object of life

In life physical forces are controlled largely by chemical transformations Energy results from chemical exchange and is comprised of two factors 'intensity and capacity factors Chemical energy can be converted into other forms without passing through heat just as it does in a battery Faraday demonstrated that the quantity of electricity obtained from a Voltaic cell is proportional to the amount of chemical

change Bayliss (") believes that chemical energy is the quantity of a substance capacity factor multiplied by its chemical potential or affinity and that the capacity factor of chemical and electrical energy is proportional and further that the intensity factors are also proportional In other words he agrees with Faraday in regarding electrical force and chemical affinity as one and the same thing

The transformation from chemical to dynamic energy appears to the writer a fruitful field for investigation The chemistry of nutrition is relatively well understood but the conversion of chemical forces into energy and activities so vital to life are poorly understood Heats of combustion do not entirely suffice They do not render accurate information as to the energy available in the organism Bayliss says for example that it is necessary to know if calorie for calorie carbohydrates have a greater energetic value than fats Such information would render dietetics of infinitely greater value

The problem is difficult but fundamental One great difficulty is the number of factors to be considered and the consequent complexity

The amount of metabolism controls the amount of oxygen needed The amount of oxygen needed controls the work of the lungs and heart respiration and circulation Thus the fast heart of exophthalmic goitre and of fever is due to increased rate of metabolism and the slow pulse encountered during starvation in the diabetic is probably due to a decreased rate of metabolism

Influence of the Nervous System

In early embryonic life nutrition is carried on without the existence of a demonstrable nervous system but at an early stage of development the nervous system begins to exert an important influence on the processes of growth and development This is most strikingly evidenced perhaps in the function of growth in anterior poliomyelitis The mind naturally turns to the question of trophic nerves Unquestionably interference with the nerve supply to a muscle may be followed by atrophy but the atrophy is not of necessity due to the nutritional disturbance occasioned directly by lack of proper nerve supply Herpes zoster is difficult to explain otherwise than on the basis of direct influence of the nervous system involving metabolism of the part supplied The possibility of direct nervous control of metabolism cannot be denied but on the other hand proof of the same is still lacking The growth of tissue in Locke's solution outside of the body proves the possibility of nutrition and growth aside from nervous influences

The blood supply to a part unquestionably plays a determining role in its metabolism and thus indirectly at least the nervous system is

important It is possible that vasomotor control is a principal factor through regulation of blood supply

The question of the role of the nervous system is deserving of the greatest consideration The intimacy between the sympathetic systems and the ductless glands suggests related functional activity Before the days of hormone activity' attempts were made to correlate the activities of the various endocrine glands through nervous channels Difficulties encountered in establishing such relationships made it necessary to look elsewhere with the result the discovery of hormones

Emotions

Similarly emotions fright anger and pain, which heretofore have been looked upon as nervous or mental attributes have assumed within later years a much broader aspect One hormone at least is of great importance in this connection Additional information concerning the function of the sympathetic system and endocrine glands must precede a solution of many questions of nutrition and metabolism

Since the nervous system is one of the controlling factors in the function of the endocrine organs it must of necessity play a leading role at least indirectly In the absence of the nervous system normal function is impossible

The endocrine glands play a leading role in the control of metabolism nutrition and growth and bodily dynamics The most important are the thyroid suprarenal and pituitary glands The influence of drugs in this connection, though marked has never been satisfactorily explained from a fundamental point of view The influence of adrenalin and to a lesser extent of strychnine and caffeine in removing the feeling of physical exhaustion as the result of prolonged work is intimately associated with the question of dynamics and energetics The work of Cannon [48] and Crile [49] on internal secretions and emotions brings the problem into the limelight and indicates its importance In these fields fundamental processes are being revealed and the foundation of science being laid on which will be built the medical treatment of the future

The Relation of Thyroid Function to Metabolism and Disease

So long as the thyroid is normal in size and function it is of no particular interest to the practicing physician Meckel in 1806 noted that it enlarged during menstruation and pregnancy which suggested a close relationship between it and the female gonads The first important contributions to our knowledge of the thyroid were made by practicing physicians In the posthumous writings of Parry [50], 1825 a fashionable physician of Bath is a description of eight cases of "Enlargement

of the Thyroid Gland in connection with Enlargement or Palpitation of the Heart In describing the first cases 1786 he writes The eyes were protruded from the sockets and the countenance exhibited an appearance of agitation and distress especially on any muscular movement The pulse rate was 150 *In speaking of the heart he says It was so vehement that each systole of the heart shook the whole thorax* The salient features the rapid overacting heart the exophthalmos the struma and the anxiety are all clearly depicted It is extremely interesting to note that the dynamic and stress features are portrayed in the original description Graves ([51]) a great clinical teacher and Basedow ( ) a general practitioner also described the same disease in 1835 and 1840 respectively Graves original description being A lady aged 21 became affected with some symptoms which were supposed to be *hysterical* *After she had been in this nervous state about three* months it was observed that her pulse had become singularly rapid Basedow was the first to attempt a physiological explanation of the manifestations of exophthalmic goitre

Many years later in 1873 Gull ([5]) another noted English physician *described the condition known as myxedema and in 1877 Ord* ([6]) established its relationship to thyroid activity Some six years later Kocher ([55]) described a cachexia strumapriva occurring in thirty per cent of cases after the removal of thyroid in goitre but this was a year after *the Reverdins had described the same condition under the name* myxedema post operatoire Still later von Brunn established the relationship of cretinism to decreased thyroid activity The early experimental work blocked rather than aided progress until the functions of the parathyroid were established and this factor covered in experimental surgical *procedures * Schiff ([6]) and Horsley ([67]) both demonstrated that trans*plantation of the thyroid prevented the effects of removal Finally came the discovery of Murray ( ) and of Howitz that feeding of the gland results in the cure of myxedema

The thyroid is an extremely vascular ductless gland a single organ composed of two lateral frequently unsymmetrical masses or lobes connected by a transverse median band or isthmus Its nerves are probably all derived from the sympathetic and accompany the arteries to the gland The true thyroid develops as an unpaired hollow outgrowth from the foregut ventrally *to the branchial arches and in the middle line* It has its origin therefore from the epithelium of the buccal cavity

Function of the Thyroid—It exercises an important control over the processes of nutrition of the body and especially over the nervous system

* Schiff described the results of complete thyroidectomy in animals in 1859

How is the control exerted? Several opinions have been held (1) The thyroid elaborates an internal secretion characterized by a large iodine content which is given off to the blood and lymph is transported to the tissues and there exercises a regulating function This is borne out by excision of the organ and by pathological processes leading to its destruction as evidenced by the development of cretinism myxedema and thyreopriva and by the close parallelism existing between hyperplasia of the thyroid and clinical manifestations of toxicity (2) The thyroid secretion neutralizes or destroys toxic substances arising in metabolism in the same manner that the liver overcomes the toxic properties of ammonia through converting it into urea Following removal of the thyroid toxic substances accumulate cause toxic manifestations and result in death For support of this hypothesis proof is entirely lacking (3) Still another view was put forward by Cyon and is deserving of some consideration On account of its extreme vascularity he believes that it acts as a vascular shunt or flood gate to protect mechanically the circulation in the brain This is reflexly effected through the hypophysis cerebri and the vagi This theory though unacceptable in its entirety recognizes the relation of the thyroid and its internal secretion to distribution and the total blood supply In the present state of knowledge it is probable that the thyroid does control blood supply not directly but secondarily through control of the rate of metabolism *It is metabolism which controls the work of the heart* *The vascular phenomena of exophthalmic goitre may be looked upon as resulting from correlated influences on the vasomotor mechanism* The heart works at its maximum and the peripheral circulation is thrown wide open to provide a maximum blood supply

The point of contact or seat of action of the internal secretion has not yet been determined Whether thyroxin acts directly on the cells of the body or through their nerve supply still remains to be settled

The body is like the social organism at large "no man liveth unto himself alone The function of the thyroid is internally related to the *function of the body as a whole* *Disturbance of its function* disarranges function as a whole Medicine has adopted an anatomical viewpoint in relation to disease But for a true grasp of disease and its manifestations this functional conception is a requisite

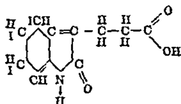
In treatment of diseases of the thyroid the fundamental question is not so much whether it is an adenoma colloid goitre or exophthalmic goitre but whether or not the active principle of the thyroid is over stimulating or failing to stimulate metabolism in other words whether we are dealing with hypo or hyper activity or perversion of function

Obviously it is desirable to know the nature of the active principle

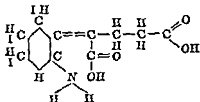
of the thyroid and the mechanism of its action Recent work has shed much light on the former subject

Chemistry of the Thyroid —Kocher with his vast clinical experience in goitre surmised that the thyroid contained an iodine combination because of the clinical effects of iodine preparations on goitres In 1896 Baumann ([59]) isolated a colloid substance which he called iodothyreoglobulin demonstrated its organic character that the gland contained several milligrams of iodine and further that the thyroid was several times richer in iodine than any other tissue of the body Subsequently through the work of Ostwald the protein nature of the compound was revealed The desiccated gland was found to be largely composed of this material and its activity was in proportion to its iodine content

The brilliant work of Kendall ([61]) has resulted in the isolation of the active principle of the thyroid in crystalline form and in the recognition of its chemical nature In describing the compound Kendall says Analysis has shown that it contains an indol group with the iodine undoubtedly attached to the benzene ring and ' that on the carbon atom adjacent to the amino group of the indol ring there is an oxygen atom He ascribes to it the formula



He lays emphasis on the oxyindol nature of the compound and on the CO and NH radicles and not on its iodine content The substance was named thyroxyindol or thyroxin for short The importance of the CO and NH groups is revealed by the disappearance of the characteristic physiological properties on substituting an acetyl group for the H of the amino radicle Investigation of the acetyl derivative showed that in alkaline solutions the indol form of the compound no longer exists but that there is hydrolysis of the CO and the NH groups resulting in the opening of the ring and the formation of COOH and NH



Further investigation showed that the thyroxin behaved in the same way and that it exists within the body not in the closed ring form such as is present in indol but in the form of COOH and NH '

This obviously accounts for the failure of physiological activity on substituting an acetyl group for the H of the amino radicle Kendall further calls attention to the analogy between the open and closed forms of thyroxin and the open and closed forms of creatin and creatinin and states that the same relation exists between amino acids per se and the form in which amino acids exist united in protein He considers the CONH and the $COONH_2$ nuclei important desiderata in the production of energy in protein metabolism Synthesis of the product has been accomplished the resulting compound exhibiting all the chemical and physiological properties of the substance isolated from the gland

The question naturally arises does the thyroid synthesize thyroxin or does it serve merely as a storage and distributing center as the liver does for instance in relation to glycogen and dextrose? The available facts are (1) the iodine is found in the gland in large quantities (2) that the quantity is variable even in health, (3) that it exists in colloidal state as a protein combination iodothyreoglobulin, (4) that this latter is not a chemical entity (5) that the desiccated gland varies in its iodine content and its activity is dependent quantitatively upon its iodine content (6) that the iodine content of the thyroid varies in disease (7) that a definite chemical entity thyroxin has been isolated from the gland in crystalline state (8) that thyroxin counteracts the effects of thyroidectomy in animals and in extremely small quantities causes striking improvement in human cases of myxedema and of sporadic cretinism, (9) that its effect in raising metabolism is quantitative in character reaching its maximum after an appropriate dose only after some days and persisting for some weeks after a single injection (10) that its activity is not dependent entirely on its iodine content Whether the hormone of the thyroid is synthesized or merely stored in the gland has not yet been determined and must be left to the future to decide

Little is known as to the mechanism of action of the thyroid The smallness of the dose of thyroxin and its marvelous effect in accelerating metabolism naturally suggests catalysis Catalytic differs from enzymatic activity in that the latter is destroyed at relatively low temperature and is as a rule markedly specific in character

The characteristic actions of a catalyst are (1) that it accelerates chemical action (2) that relatively small quantities suffice and beyond certain limits further increase in the catalyst does not further accelerate the action (3) that it acts only by its presence and it does not itself participate in the reaction (with certain exceptions) or at least it does not

form part of the resulting system in the final equilibrium (4) that it acts over and over again and that as a rule it is destroyed or removed from the sphere of action in the form of constituents of some of the subsidiary reactions (5) and that when the system is one that reaches a definite equilibrium under the conditions of the experiment the position of this equilibrium is unaffected by the presence or the amount of the catalyst which merely hastens the time taken by the process and this in proportion to its concentration up to a certain point

Two important things are shown by these facts namely that the catalyst does not supply or remove energy from the system and that it accelerates both the hydrolytic and synthetic components of a reversible reaction Thyroxin fulfills most of these requirements in that it increases the rate of metabolism acts in small quantities increasingly more with somewhat larger quantities acts over a period of some weeks from a single dose so that in all probability it acts repeatedly and finally in that it does not modify the type but only the rate of metabolism so far as can be ascertained Against its catalytic activity can be argued the slowness with which its effect is exerted the maximum not being reached for several days and the evident dynamic effect in increasing the energy of the individual The latter however is secondary not the result of the increase of the chemical reaction per se but of the restoration of normal function as the result of normal metabolism

The seat of action of the active principle of the thyroid is still a matter of discussion Is its function carried on in the gland through the nervous system or in the cells of the body generally? It seems probable that the gland acts as a storehouse and gives off the active principle which acts as Plummer believes on the cells of the body generally both directly and indirectly

The gland itself is subject to control It is influenced by other glands of internal secretion and also by the sympathetic nervous system The work of Cannon in which overactivity of the thyroid was obtained through continuous stimulation of the sympathetic through transplantation of the phrenic into the cervical sympathetic established the importance of the sympathetic system in relation to the function of the thyroid

Clinically the anamnesis of exophthalmic goitre is usually a history of prolonged nervousness Its clinical manifestations include many and marked evidences of the involvement of the sympathetic Barker says

Among the symptoms largely referable to the autonomic nervous system are included (a) the eye signs (b) the cardiovascular phenomena (c) the cutaneous phenomena (d) the digestive disturbances (e) the *respiratory disturbances and (f) the urogenital symptoms*

Similarly, infection local or general exercises a marked influence on the thyroid and upon metabolism This knowledge is born of clinical experience which reveals the closest connection between acute or chronic infections and manifestations of Graves disease

Before discussing the diseases of the thyroid, a survey of the clinical manifestations *following the removal of the thyroid and those of Graves* disease cannot fail to impress one with the significance of the role of the thyroid In fact the contrast was in large part responsible for the present day view that the thyroid itself through overactivity is a primary factor in Graves disease Kocher has tabulated the following facts

Cachexia Thyreopriva	*Graves Disease*
Absence of atrophy of the thyroid gland	Swelling of the thyroid gland usually of a diffuse nature Hypervascularization
Slow small regular pulse	Rapid full and at times irregular pulse
Cold skin without flushings	Irritable vasomotor system
An uninterested quiet stare without expression of life	Anxious appearance angry expression
Narrow palpebral aperture	Wide palpebral aperture exophthalmos
Slow digestion and excretion poor appetite requiring little food	Abundant excretions an excessive appetite with increased needs of food
Retarded metabolism	Increased metabolism
Skin is thick opaque folded dry and scaling	Skin is thin transparent finely injected and moist
Short thick fingers with broad ends	Long slender fingers with pointed ends
Sleepy	Wakeful and disturbed sleep
Dulled sensation apperception and action	Increased sensation apperception and action
Lack of thoughts interest and emotion	Flight of ideas psychic excitation even to hallucination mania and melancholia
Slow awkward muscular movements	Constant activity and haste
Stiffness of the extremities	Tremor and increased mobility of joints
Delay in growth of bones often with deformities Bones thick and soft	Slender skeleton with here and there soft bones
Constant chilliness	Unbearable feeling of heat
Slow deep breathing	Superficial breathing with imperfect inspiratory expansion
Increase in weight	Loss of weight
Aged appearance even of young people	Youthful appearance especially at the onset

Hypothyroidism —There are three types of hypothyroidism The first described was spontaneous myxedema As already indicated surgical removal of the thyroid in goitre led to the recognition of myxedema post operatoire' while later cretinism was recognized and also its relationship to the thyroid According to Osler credit is due to Felix Simon for recognizing that these were all one and the same disease and all due to loss of function of the thyroid gland They have in common nutritional disturbance mental retardation changes in tegumental structures and edematous or mucous deposits

Myxedema may occur spontaneously or subsequent to operative removal of the thyroid The name *myxedema was employed because of* the peculiar edematous like swellings observed in the cutaneous and sub cutaneous and other tissues These swellings differ from ordinary edema in that they are firmer and do not pit on pressure and in that histologi cally they show a mucin like material

The disease is characterized according to Ord who established its etiology by marked increase in the general bulk of the body a peculiar *firm swelling or edema of the skin which does not pit on pressure dry* ness and roughness of the skin (which together with the swelling tends to obliterate the normal lines of the face thus resulting in a peculiar physiognomy which is often pathognomonic) and finally imperfect nu trition of hair and nails The features become coarse and expressionless and the skin takes on a pallid waxy appearance In addition to physical changes there is generally marked mental retardation suggesting stupid ity at times lethargy and *somnolence* Slowness in movement is also striking Patients complain bitterly of being cold This is worse in cold and less troublesome in warm weather

The onset is insidious slowly progressive resulting eventually in most instances in the bodily changes already described and in asthenia loss of capacity for work and a susceptibility to marked mental changes involv ing suspicions delusions hallucinations and occasionally dementia Instances of both hyper and hypo-activity of the thyroid have been noted from time to time Myxedema has also been encountered subsequent to exophthalmic goitre and in the later stages of adenoma of the thyroid

The postoperative condition is infrequent in this country After com plete thyroidectomy it occurs in seventy five per cent of cases according to Kocher who advises that at least one-quarter of the gland be left if possible Its features are identical with those of myxedema proper It follows operations in which a large proportion of the gland is removed and occasionally in less marked resections in patients who have exhibited dysthyroidism

Skeletal changes such as are seen in cretinism are rare except in cases developing in youth subsequent to one of the febrile diseases Through studies of the rate of basal metabolism decreases of from ten to thirty per cent are revealed Formerly such studies were possible only in special institutions but now that indirect calorimetry has been made simple and reliable studies of metabolic rate are being made in many clinics through out the country

Cretinism—Of this there are two forms the sporadic and the endemic only the former occurring in America The condition may be congenital due to absence of the gland or acquired due to atrophy

resulting from one of the febrile affections It is encountered not infrequently It is characterized by bodily and mental retardation and by certain skeletal deviations which are more or less characteristic and which indicate that the thyroid secretion plays a role in relation to growth and mental development

Recognition of the condition is usually not made before six months of age, while the disease is well marked at the end of the first or in the second years The head is deformed in sporadic cases long in the antero posterior diameter (dolichocephalic) The body is undersized dwarfed pudgy and the abdomen protuberant The face is that of an imbecile the mouth open the tongue large and protruding and the bridge of the nose sunken The fontanelles close late and the epiphyses unite with the long bones late or not at all The hands and feet are thick and stubby Dentition is delayed Marked weakness exists so that the child cannot support itself The skin is thick pallid and waxy, the hair thin and subcutaneous pads such as are seen in myxedema occur at times especially about the cheeks Mentality is markedly retarded and in some instances imbecility develops

Once the condition has been seen it is readily diagnosed as a rule The facial expression the skin changes the protruding abdomen and the physical and mental retardation at once suggest cretinism Metabolic studies reveal a lowered metabolic rate decrease of ten to forty per cent below normal

Treatment of Myxedema and Cretinism —The progress in the treatment of myxedema exemplifies the rapidity of the development of the science of therapeutics Results regarded as impossible a century ago as marvelous two decades ago are accepted as a matter of course today Just as salvarsan overshadows the mercury treatment of syphilis so thyroxin supplants older methods owing to its efficacy its rapidity and the manner in which it lends itself to quantitative study and control To revert to the terminology of proprietary medicine the results are startling In some instances individuals are made over overnight No more brilliant therapy exists in the healing art today than in deficiency of the thyroid gland

The fresh gland desiccated powder aqueous and glycerine extracts are all efficacious in the majority of cases of myxedema Numerous preparations of gland are marketed but the most convenient are the desiccated gland and the glycerine extract The powdered gland is given in 0 065 gm , or one grain doses three times a day in the beginning and increased to 0 651 gm or 10 to 15 grains per day Unpleasant symptoms irritation of the skin restlessness tachycardia and delirium and in some instances tonic spasms sometimes accompany its use In the majority of

instances no untoward effects are encountered Within a few weeks the marvelous changes referred to above appear The skin becomes soft warm and natural the edema disappears and the face is that of another individual No less striking is the change in character and deportment from the slow cumbersome sluggish victim of myxedema there emerges a normal wide awake individual

Following the initial intensive treatment subsequent intermittent treatment with small doses is necessary in most cases of myxedema and in all cases of cretinism Relapse usually follows prolonged absence of the drug

Treatment with thyroxin is a matter of science It deals with accurate measurement of the drug of the rate of metabolism of the time element and with the control of effects After determining the metabolic rate the dose is calculated according to the percentage decrease of metabolic rate The number of milligrams of thyroxin required is *treated with 10 per cent NaOH diluted with distilled water and administered* intravenously With marked lowering of metabolism (25 30%) 10 to 15 milligrams are used while with a slight decrease (10-20%) 5 or sometimes 10 milligrams are used Each milligram according to Plummer raises metabolic rate two per cent Metabolism usually reaches its maximum on the 8th or 12th day maintains a plateau and then gradually decreases However the writer has observed a rise from below twenty seven per cent to normal metabolism in five days on administering five milligrams in a single dose intravenously

Although the maximum effect on metabolism is not immediate that on the patient may be Cases typical in every respect may be absolutely revolutionized within twenty four hours Plummer who was the first to use thyroxin relates his great surprise on his first visit subsequent to treatment He doubted his own eyes On the other hand metabolic rate may be brought to normal without striking concomitant clinical results as in one of our own cases

Large quantities of urine sometimes amounting to several liters are not infrequently passed during the first twenty four hours and with the polyuria the edema or myxedema of the skin and subcutaneous tissues disappears Palpitation is apt to be a striking phenomenon Headache is frequently a marked symptom and occasionally vomiting In the majority of cases the patient appears to be feels acts and is a different individual The skin resumes its softness perspiration is reestablished and the patient feels warm again sometimes after being cold for years

The time relationship between this recovery of the patient and the return of metabolism to normal is a matter of great interest but no

explanation is yet apparent Subjective and objective improvement may precede the maximum metabolic rate by at least a week

The treatment in cretinism is identical in every respect except that smaller doses are employed A cretin treated with thyroxin by us was converted within a short period from a slow stupid imbecile to the liveliest and most interesting youngster in the ward, the result of two injections of 2 mgms each

Hyperthyroidism—Before considering hyperthyroidism clinically it is well to obtain a view of its experimental aspects Two general methods have been employed in its production

(1) The administration of thyroid In sufficient doses toxicity appears in all animals but is most readily produced as a rule in the human Carnivorous animals are least affected In man loss of weight is one of the most constant manifestations, the result apparently of increase in metabolism Skin changes are common especially sweating which is accompanied by a general feeling of warmth Tachycardia is of common occurrence as are also restlessness irritability, excitability and insomnia Trembling is frequent and gastrointestinal disturbances common These symptoms are observed not infrequently in the clinical use of the desiccated gland and lead to its discontinuation Motthafft s patient mentioned by Hewlett a fat man of 43 years who took about 1 000 tablets in the course of five weeks developed rapid respiration slight fever, glycosuria and bilateral exophthalmus in addition to the usual manifestations listed above This is perhaps the nearest approach on record to the experimental production of exophthalmic goitre Exophthalmus is also reported by Beclere

In animals emaciation increased appetite thirst, digestive disturbances and exophthalmus have been produced Glycosuria has resulted in some instances *Increased metabolism is a constant* feature Similar effects have followed the administration of iodine to patients suffering from disease of the thyroid loss of weight nervousness tachycardia and tremor being the most common manifestations These are not ordinary evidences of iodism such as are seen in normal individuals and they probably result from the effect of iodine on the diseased thyroid

(2) Thyroid stimulation through the sympathetic nervous system Cannon and his associates have produced hyperthyroidism in a manner which sheds considerable light on the mechanism involved The phrenic was cut in the neck in cats and its peripheral end was anastomosed into the central end of the cut cervical sympathetic Subsequent to union stimuli from the constantly active diaphragm supplied the sympathetic with constant stimulation Increased excitability tachycardia diarrhea

exophthalmus and high rate of metabolism were induced The symptoms bore a striking relationship to those of hyperthyroidism

Before leaving the subject of the effects of the thyroid on metabolism and growth the brilliant studies of Gudernatsch should be mentioned This investigator fed thyroid to tadpoles and showed that this resulted in stunting of the growth of the animal but in early metamorphosis The limbs appeared early and the tail disappeared earlier than normal long before the tadpole had attained the size at which this usually occurs These results are in keeping with our general ideas concerning the direct relation of the thyroid to growth of the soma and gonads

Exophthalmic Goitre—Hyperthyroidism is most frequently associated with exophthalmic goitre or toxic adenomata The former is a disease characterized by goitre exophthalmus tachycardia tremor nervousness and increased metabolic rate associated with a perverted or hyperactive state of the thyroid gland

The condition has been looked upon by many as a pure neurosis because of the prominence of nervous manifestations in the anamnesis and in the disease itself and because of its development in many instances after nervous and emotional strains At present it is usually accepted as a disease of the thyroid the result of hyperactivity The gland in exophthalmic goitre suggests great activity extreme vascularity with increased proliferation and with the production of newly formed spaces and absorption of the colloid material which is replaced by a more mucinous fluid The importance of the thyroid itself is borne out by partial thyroidectomy which yields much better results than any other treatment as yet suggested With the removal of thyroid substance the metabolism returns rapidly to normal and the symptoms disappear If too much thyroid tissue is removed evidences of myxedema develop which in turn can be removed by administration of the desiccated gland or thyroxin On the other hand the disease can be produced experimentally through nervous influences as demonstrated by the work of Cannon It must be admitted that at the present time the seat of the primary change has not been determined

The disease is one of adult life rarely appears before puberty and affects females more than males Its course may be acute but is usually chronic The main clinical manifestations will be considered in some detail especially their pathogenesis in order to learn something of th mechanism involved in the disease

Barker classifies the symptoms of Graves disease as follows (1) the goitre or struma (2) symptoms referable to the autonomic nervous system including (a) eye signs (b) the cardiovascular phenomena (c) the cutaneous phenomena (d) the digestive disturbances (e) the

respiration disturbances (f) and the uro genital symptoms, (3) meta bolic disturbances (4) symptoms referable to other endocrine glands, (5) cerebral symptoms and (6) blood changes

The gland is usually enlarged symmetrically but not necessarily so It is extremely vascular as evidenced by thrills and bruits Its low iodine content is difficult to explain except on the basis that the gland ordinarily stores iodine which function is lost in hyper activity

In typical cases metabolism is greatly increased in some cases fifty to eighty per cent above normal This increase is exaggerated by extreme nervousness by bodily and mental overactivity These are prob ably but factors in a vicious circle The skin is usually warm and moist and fever is not at all uncommon In addition to total metabolism change occurs in relation to carbohydrates and proteins

Tissue catabolism is marked resulting in increased nitrogen excretion and in loss of weight Nitrogen equilibrium is difficult to maintain Alimentary glycosuria is common The explanation for this is not clear but the work of Cramer and Kraus suggests the possibility of it being a deficiency in the glycogenic function of the liver

The possibility of the tachycardia being due to stimulation of the accelerator nerves of the heart is not at present entertained In all probability it is but a part of the cycle involved in increase in metabolism The heart is overactive in order to supply sufficient blood to the over metabolizing tissues generally The rapid circulation the overacting heart the high systolic and low diastolic pressure the high pulse pressure capillary pulsation and vascular erythema are all incidental features involved in the effort to supply sufficient blood The development later of myocardial insufficiency of dilation and arrythmias are but natural sequences of overuse If the cardiac control is of nervous origin this is probably secondary to metabolic states

The exophthalmus is probably due to relaxation of the extra ocular muscles or to spasm of the smooth muscle fibers described by Muller Their function in contraction is to protrude the eyeball and pull back the lids and it is carried out through fibers from the cervical sympathetic The possibility of localized edema of the orbit seems unlikely to the writer though the presence of fat as the explanation of the failure of disappearance of exophthalmus after cure in long standing cases appears quite reasonable

The tremors are unexplained unless they are accepted as evidence of the tense overwrought nervous system or secondary to concomitant involvement of the parathyroids The nervous manifestations indicate that the nervous system is involved in the process primarily or second arily They appear early as a rule and occasion great discomfort to

the patient As already indicated they frequently result from the administration of thyroid Increased metabolic rates such as are encountered in febrile conditions are not infrequently also accompanied by similar nervous symptoms (Barker)

The disease is one of several years duration After persisting several months symptoms may disappear to reappear again at a later date Clinically the effect of infections is most striking Thus a mild attack of tonsillitis may occasion an acute marked exacerbation of the Graves disease which in some instances disappears as the local condition clears up or more frequently subsides slowly in the course of a few weeks or months Similarly emotions and nervous strains are prolific sources of acute exacerbation

Plausible explanations can be found for the clinical manifestation in typical cases But atypical cases abound In the early stages of the disease the diagnosis is most difficult at times In the same individual striking evidences for over and under function of the thyroid are not at all infrequent One or another feature may be strikingly exaggerated or entirely wanting It is the inability to explain the bizarre combinations of clinical findings in the individual case that makes the clinician skeptical of theories and chary of accepting one chemical entity as the active principle of the thyroid Correlations of laboratory investigations with clinical studies serve to increase this skepticism at times Normal or even decreased metabolic rates are encountered at times with clinical pictures very suggestive of Graves disease or of thyrotoxicosis

There is a feature of Graves disease that baffles expression It is revealed in the facial expression in the incessant restlessness the overwhelming nervous strain and in the pent up feeling It is kinetic dynamic a hidden fire I am always reminded by a case of this kind of a motor car gear in neutral brakes set but with the engine still running Even at rest the throb of life is evident combustion is going on energy is being dissipated or is felt but it is not being utilized and back of it all one recognizes that fuel is being consumed that energy is wasted and *that the engine is being subjected to useless wear and tear* Such factors must be approached through studies in energetics dynamics and kinetics living forces as yet but little understood

Treatment of Hyperthyroidism

(*a*) If we accept the theory of overactivity of the thyroid as the cause of exophthalmic goitre logically in the absence of effective method of control of its action we are forced to turn to partial removal of the gland Practically this procedure yields the best results But since operations cannot be lightly undertaken every effort must be made to

obtain results in other ways until such time at least as the operation appears imperative

The important features are absolute rest in bed and freedom from visitors An ice bag is placed locally over the thyroid and another over the heart if it is tumultuous Digitalis or strophanthus are indicated for myocardial insufficiency Many drugs have been advocated but few give outspoken results Cacodylate of sodium is used hypodermically for the lowering of metabolism although proof of such an effect is lacking We have observed marked decrease in metabolic rate coincident with its employment but whether it is the general treatment (rest diet etc) that played the greater role has not yet been determined

(*b*) Milk of dethyroidized goats has been tried as has also serum of animals into which human thyroid extract has been injected Some good results have been reported from both these methods but they have not sufficient effect to bring them into general use

(*c*) Dietary measures a low caloric diet with a more than proportionate decrease in proteins is desirable for a short period at least

(*d*) Local injections of urea solution into the thyroid gland is followed by improvement in some cases

(*e*) Removal of foci of infection exercises a beneficial effect at times

Ligation of vessels suffices in many cases but in the majority of instances the results are purely temporary Partial excision as practiced by many surgeons gives much the best results Recovery is rapid and complete in many cases Excision of the superior cervical sympathetic ganglia has also been practiced, the slight ptosis resulting serving to alleviate the staring expression associated with the exophthalmus

Two procedures practiced by surgeons in relation to thyroid operations are worthy of mention (1) the practice in certain clinics of observing the effect of the visit to the operating room and the postponement of the operation in the event of undue excitement with marked exacerbation of symptoms and (2) anoci association which was introduced by Crile in an effort to protect the nervous system generally from the shock of the operation These indicate the importance which the nervous system plays in the experience of the surgeon

The thymus which is enlarged in a considerable percentage of thyroid cases has been subjected to systematic X ray treatment The results as a whole have been disappointing Systematic and prolonged treatment of both thymus and thyroid has yielded some brilliant results

Here again in the treatment of thyroid disease the basis for future drug therapy is being laid With increasing knowledge of metabolism chemical control of these processes will be sought Means of chemically

increasing the rate of metabolism have already been attained The problem of finding chemicals capable of slowing the rate of metabolism now confronts us

(7) Treatment Based on a Functional Conception of Disease

A functional conception of disease as a basis of treatment is rapidly attaining a foothold in medicine From the vast field presented only one example will be considered This however will be discussed in considerable detail since through such a procedure the various principles underlying this form of treatment can be presented

Myocardial Insufficiency

The function of the heart is to keep the blood circulating sending it (1) to the lungs where it rids itself of its CO_2 and takes up oxygen (2) to the tissues where it supplies oxygen and nutriment and takes up waste material (3) to the gastrointestinal tract where it receives nutriment and (4) to the organs of excretion which remove waste products The heart must efficiently maintain circulation which involves a sufficient minute volume output and an adequate blood pressure The factor of safety or reserve force of the heart is great The guiding principle of treatment is restoration of reserve force The muscle power of the heart is the chief concern of the therapeutist

Harrington Sainsbury ([61]) emphasizes this in a most charming and forceful way in the prologue to his little volume Principia Therapeutica in a dialogue between the pathologist and internist parts of which the author was wont to use in beginning his course of lectures in therapeutics

Path The apothecary tells me there is a long bill on account — digitalis strophanthus sparteine and Heaven knows what more for I could not outstay the tale of the remedies employed Friend what had you in mind and what was the real task before you could you but have seen? See here this aortic valve which you rightly diagnosed to be narrowed it scarcely admits a thin pencil—and the valves if you can call them such fused and thickened as they are and hard as a piece of Roman mortar they do not look exactly amenable to treatment did you think to soften them? And this heart muscle its fibers stretched and degenerate what hope was there? Doubtless you proposed to make new fibers to overcome the destruction? What a commentary upon the drug list is here!

Phys Not mine the fault for as you say I did not spare the drugs

but proceed—this case of stenosed aorta which you have so accurately described was taken from the body of a woman Can you favor me with her age?

Path Seventy six '

Phys ' Precisely and her history tells I think that though always ailing her symptoms did not point definitely to failing heart until after her sixty seventh year The rigid valves are so thickened that the orifice is reduced to a mere chink Could you perhaps give a date to this calcification? '

Path That would be difficult it is certainly not of yesterday

Phys The change has clearly been of slow development and I think you will admit that its first beginnings may date back many years perhaps to infancy and that in this extreme form it must have existed for many months

Path Agreed

Phys And yet symptoms have been so surprisingly absent But you are well aware this is no isolated occurrence and cases as extreme as this have been entirely latent through a long life and have proved compatible even with seeming good health This was so in a case which I have in mind in which the patient also a woman again reached the age of seventy six '

Path Need we elaborate this portion of the argument?"

Phys 'Willingly I pass on but first let me very briefly insist upon the inference viz that this specimen declares vitality not mortality Here for instance is a vital organ irreparably damaged at the fountain head so to speak and yet the patient outlives her three score years and ten

By what means? You have called attention to the dilated chambers of the heart and to the stretched and degenerate fibers of the muscular walls you have confirmed these degenerations by the microscope and you have admitted I think that these same changes give clear evidence of long standing and that some of them e g the dilations must reach back in their beginnings to the first changes in the damaged valve thus you have borne witness to an inadequacy declared and long prepared Not by virtue of these but in their despite has life been prolonged and yet the patient attains to the age of seventy six By what means?

' Surveying the whole case and placing upon the one side the work to be done the mass of blood to be moved the obstruction to be overcome and upon the other available forces of the heart muscle we must confess I grant it, that the latter *appear* wholly unequal to the task Yet the sum of it all is a long life Will you think me unreasonable if I claim this heart is an instance of triumph not of failure? '

Myocardial insufficiency arises from many causes In its chronic form it is caused by myocardial changes or lesions lesions of the valves lesions affecting the vascular fields of the efferent arteries overexertion poisons especially alcohol (beer) adherent pericardium goitre and Graves disease Numerous anatomical bases such as coronary sclerosis interstitial myocarditis fragmentation and segmentation parenchymatous degeneration fatty or amyloid degeneration and lesions affecting the bundle of His can be ascribed as the underlying cause Hypertrophy or dilation or both may exist Hypertension alone or in combination *with nephritis is frequently associated with the myocardial insufficiency* But irrespective of the nature of the cause or of the lesion or of associated complications *the important desideratum is restoration of myocardial function*

But what are the functions of the heart muscle? They depend on its cardinal properties which are five in number contractility (inotropism) conductivity (dromotropism) irritability (bathmotropism) rhythmicity (chronotropism) and tonicity Cardiac function may be disturbed in relation to all or one or a combination of these properties recognition of which markedly affects the efficiency of treatment since treatment can be directed especially in some instances towards one or more of these derangements Digitalis in therapeutic doses affects tonicity conductivity and contractility In toxic doses irritability is greatly increased and rhythmicity markedly disturbed

A word might be said concerning renal function in myocardial insufficiency since it must be considered in the treatment of this condition

Myocardial Insufficiency and Renal Function ([2]) —Myocardial insufficiency may occur independently but in a large proportion of cases it develops in association with nephritis It is often impossible on purely clinical lines in an individual case to decide whether the kidney or heart is primarily responsible for the clinical picture encountered In this connection renal functional studies are of the greatest assistance

Marked renal insufficiency may result from pure chronic passive congestion Very exceptionally clinically and experimentally the functional studies reveal a decrease in function equaling that seen in the most severe grades of nephritis Since the congestion to effect this must be of a most extreme grade death is imminent on account of the heart As a rule in myocardial insufficiency with a symptomatic and urinary picture identical with that seen in a moderately advanced nephritis alone or in nephritis associated with a cardiac break renal function as indicated by both excretory and retention tests is surprisingly good When low renal function is followed by an increased phthalein output the amount of increase gives a fair approximation of the extent of cardiac improvement

In this connection also urea and total non protein nitrogen studies are of great value In pure passive congestion an increase in total non protein nitrogen above 50 mg to 100 c c of blood is extremely rare In only three instances among several hundred cases studied has the author encountered it Foster has lately reported three more instances Blood creatinine is rarely significantly increased in pure passive congestion of the kidney The finding of normal nitrogen figures therefore is of considerable diagnostic significance A phthalein rapidly returning to normal associated with a low level of blood total non protein nitrogen and urea speaks strongly for passive congestion as the underlying process

Treatment of Myocardial Insufficiency —Myocardial insufficiency constitutes a pathological indication for treatment and calls for treatment notwithstanding other conditions present The principles underlying this treatment are rest limited diet limited salt and fluid intake depletion through bleeding purgatives diuresis or paracentesis and support of the heart In addition certain symptoms may call for special attention

In many instances the general treatment is more important than drug therapy On the other hand drugs are of unquestionable value frequently playing an important role In this article detailed consideration can be allowed only drug therapy

Rest —This is essential and must be complete at first absolute rest of short duration In long continued chronic myocardial insufficiency absolute rest is of course impossible A back rest often affords great comfort An additional reason for absolute rest is found in the serious consequences which may attend exercise in a patient under the influence of digitalis

Diet —This must be restricted in three ways as to (1) the quantity taken at one feeding (2) the salt content and (3) water intake Rest for the stomach as well as for the heart must be insisted on Do not overfeed This is a good rule often broken

Fluids —The intake of water and fluids should be restricted the more the edema the greater the restriction A special fluid chart indicating the fluid intake and the urinary output should be kept in all cases with marked edema The total fluid intake should be limited to 1 to 1 5 liters a day at first more fluid being allowed as diuresis is established and edema disappears Enormous quantities of water may be lost in the course of a few days a decrease of 20 to 30 pounds in the course of 5 to 6 days not being infrequent In one of the author s cases 70 pounds were lost in one week anasarca disappeared and the phthalein output increased from sixteen per cent to normal

Sodium Chloride —Widal has shown how important is the restriction

of sodium chloride In the diet the salt content must be small An absolutely salt free diet is practically impossible and is not necessary It is next to impossible to obtain a salt content less than 1 gm a day Milk contains 0 16 per cent sodium chloride so that any diet containing milk of necessity contains some salt

So great restriction of salt is often not advisable over prolonged periods The guide to the amount allowed is found in the ability of the kidney to excrete it Where fair amounts are excreted and particularly where its concentration in the urine is good more can be allowed Many patients are kept on a salt free diet long after the necessity of it has passed Great quantities of salt are excreted as a rule with the clearing up of edema and anasarca Prolonged use of salt free diet may lead to deprivation of the tissues of sodium chloride

Methods of Depletion—Bleeding tapping of the pleural pericardial or abdominal cavities diuresis and purgation may all be indicated at times Sweating is contraindicated owing to the strain involved upon the heart

Bleeding—Venesection is indicated in acute dilation of the heart particularly of the right heart

Purgation—This is employed in practically all cases of outspoken myocardial insufficiency It is useful for the removal of water for the *removal of putrefactive material from the intestine and also for the* relief of intestinal distention It may be employed without fear even where asthenia is marked and the pulse feeble Hydragogues should be used Magnesium sulphate 16 to 48 grams (½ to 1½ ounces) given in concentrated form each morning on an empty stomach is the most satisfactory method of inducing purgation in the majority of cases This usually results in two or three large fluid stools each day When this is not well borne by the stomach i e when it occasions nausea and vomiting 1 or 2 compound cathartic pills each night or compound jalap powder 1 to 3 gms (15 to 40 grains) or compound elaterin powder 3 to 6 gms (1/20 to 1/10 grain) in alcohol is sometimes efficacious when other methods have failed Enemata may occasionally be necessary

After the anasarca disappears milder purgatives or laxatives such as cascara and liquorice powder may be required for regulating the intestines

Diuresis—This is usually obtained through the use of digitalis Where this is not effectual recourse is had to one of the caffeine diuretics Theocine is most satisfactory 0 2 gm (3 grains) t i d for one day The effect is noted and the drug repeated on alternate days if necessary

Support of Heart—Digitalis is the drug par excellence in this connection Introduced by Withering in 1785 for the relief of dropsy it

has become our mainstay in the treatment of myocardial insufficiency Its relation to circulatory disturbances was emphasized by John Ferrier 1799 Although a great amount of work has been done on this subject *little is yet known in a practical way concerning the chemistry of the* active principles of digitalis Undoubtedly the future will furnish synthetic chemicals which ultimately will replace digitalis But in the meantime striking results can be obtained through its intelligent use

Myocardial insufficiency constitutes the indication for its use regardless of the nature of the underlying lesions Auricular fibrillation demands an intensive digitalis therapy and indeed it is in cases of auricular fibrillation that we see its most striking effects Its best diuretic effect is seen in dropsy dependent upon circulatory changes in the kidneys In the acute myocardial involvement of acute febrile diseases the usefulness of digitalis is rather limited Once circulatory collapse supervenes results are meager Earlier in the disease before blood pressure is markedly depressed good results can be obtained especially in cases developing fibrillation Toxic manifestation should be carefully watched for in such conditions

Digitalis is manifold in its action It acts on the heart muscle* itself increasing its irritability tonicity and strength of contraction on the bundle of His decreasing conductivity, on the vagus slowing the rate, on the vascular system through the vasomotor center, and directly on the vessel walls inducing vasoconstriction and increase in blood pressure *It slows the heart increasing its force and the output per* beat and per minute and tends in passive congestion resulting from myocardial insufficiency to shift the blood from the venous side where it has collected to the arterial side of the vascular system In therapeutic doses it results in improved circulation through the kidney (a relative vasodilating effect upon the renal vessels being claimed), diuresis resulting It finds its greatest value in cases of mitral disease with marked edema and small rapid and irregular pulse although it is of value in all cases of myocardial insufficiency despite the nature of valvular lesion

Digitalis should be administered in courses and its use should be *intensive from the beginning irrespective of the preparation* used A single course may suffice but repeated courses are usually indicated In auricular fibrillation intensive treatment is indicated at first and subsequently after compensation is reestablished more or less continuous or

* In this connection the work of Schliomensun is extremely illuminating (*Arch f Path u Pharm* LXIII) An alcoholic phosphatid was extracted from the hearts of animals receiving digitalis therapy which when injected into a second animal produced all of the biological reactions of digitalis This he claims indicates a direct combination of digitalis with the heart muscle Similar extracts from other tissues of these animals failed to yield such a product indicating that the substance was specific to heart muscle

tonic treatment In this condition small doses can be taken almost continually or at frequent intervals for months or years Patients may feel well on this regimen who otherwise do badly

The preparations of digitalis are numerous but four stand out preeminently These are the powdered leaf the tincture the infusion and digipuratum Each preparation has its advocates Results can be obtained with any of them provided the preparation is an active one and that it is properly administered to suitable cases

The preparations most commonly used in the wards of our hospital are the infusion and the tincture The infusion is given every 3 or 4 hours for 48 hours *The infusion is an aqueous extract and contains* relatively more digitonin than the tincture As a diuretic it is particularly valuable It should be prepared fresh a new supply being obtained once a week The tincture is also excellent It is an alcoholic preparation containing relatively more digitoxin digitalin and digitophyllin than the infusion It is administered in 1 c c doses every 3 or 4 hours for 48 hours It is usually combined with tincture amygdali amari or some other bitter and administered well diluted

The powdered leaf is given in 0 065 to 0 1 gm (1 to 1½ gr) doses every 3 or 4 hours for 48 hours Digipuratum is a standardized preparation of digitalis in tablet form each corresponding to 0 065 to 0 1 gm (1 to 1½ gr) of the digitalis leaf Four tablets are given during the first 24 hours three the second two the third and one the fourth It is an active preparation and well standardized but much more expensive than any of the foregoing preparations which are equally efficacious provided they are properly standardized Digipuratum is also marketed in ampules in liquid form This preparation can be given intravenously or intramuscularly without marked irritation The ampule contains 1 c c which corresponds to 0 1 gm of the leaf

The doses given above represent the routine of the hospital It cannot be too strongly emphasized however that digitalis should not be measured in grams grains or hours but by results The chief requisites are an active standardized preparation and proper indications The former is readily obtained and is unquestionably of the greatest importance

Standardization of Digitalis—Two methods are in common use the frog and the cat method The *frog* method consists of injecting the digitalis preparation into the anterior lymph sac of a frog (Rana pipiens) and determining the amount necessary to bring about systolic standstill in one hour The results are expressed in heart tonic units This conveys no impression as to the activity of the preparation unless one knows what constitutes a heart tonic unit According to Houghton a heart tonic unit

is ten times the normal fatal dose per gram of frog to Edmonds it is the amount per 20 gm weight of frog necessary to bring about systolic standstill in one hour while according to Hale it is the amount necessary per gm of body weight A heart tonic unit may therefore vary 400 per cent according to what constitutes the standard Neverthe less the standardization is of value if one accepts any standardized preparation and learns how to use it intelligently The frog method is not satisfactory for the standardization of a dilute preparation such as the official infusion, since such large quantities must be introduced into the lymph sac that absorption is often not complete at the end of an hour

The cat method of Hatcher ([63]) is simple and satisfactory The preparation to be tested is slowly run into the femoral vein of a cat until death results The number of c c per kg of cat constitutes a cat unit The technic as employed by the author in standardizing the infusion is as follows —the cat is given just sufficient ether to permit a cannula being placed in the femoral vein By means of a burette or a syringe 10 c c of the filtered infusion is injected in the course of five minutes and 1 c c every two minutes thereafter until death The total amount is noted, and the amount per kg of the cat unit is calculated

The following emphasizes the importance of standardization Leaves from various sources (German English and American) obtained for the hospital pharmacy infusions were prepared according to the United States Pharmacopoeia Macht ([64]) and the writer found that some of these infusions required only 6 to 7 c c per kg whereas others required 10 and 12 and one (the German leaf) required 23 c c per kg to kill the cat A variation of 400 per cent was therefore found in leaves in the hospital pharmacy Before leaving Baltimore the writer introduced American grown digitalis (Wisconsin leaf) into general use in the wards Standardized American grown digitalis (Minnesota Washing ton and Oregon) was used extensively by the Medical Corps of the Army

Eggleston ([65]) has recently claimed that 0 143 cat units per pound of body weight constitutes the amount necessary for maximal therapeutic effects The additional claim is also made that this full amount can be given in 24 rather than in 48 hours one half being given in the first dose one third 4 to 6 hours later and small doses at 4 hour intervals until the calculated amount is reached Doses up to 50 c c of the infusion now in use in our wards have been given as the initial dose without untoward effect This method has been thoroughly tested in my wards during the last three years by Drs White and Morris ([66]) utilizing standardized American grown digitalis

Our impression is that the Eggleston method is a valuable addition in digitalis therapy that it gives confidence in the use of the drug and that the shorter time necessary for securing digitalis effects should give the method wide use Results are frequently obtained within twenty four hours

The method must be used with care to select cases in which these effects are desired Cases of acute or chronic infections with the probability of the presence of endocardial infections should be given the method if at all only after careful study because of the possibility of embolism and quite as important in our opinion the possibility of associated myocardial changes predisposing to block

The method requires careful study of the patient before during and *after its administration and since it produces powerful and clear cut* effects should be used with extreme care and judgment The digitalis effect is often secured within 24 hours

Since there are so great variations in the potency of digitalis it becomes imperative for its intelligent use that the physician be familiar with the potency of the preparation which he is administering The only other alternative is to push the drug until the therapeutic effect is obtained provided it is a case suitable to digitalis therapy

In order to do this one must have well in mind what constitutes the therapeutic stage of digitalis treatment and what criteria are to be *accepted as indicating the desired digitalis effect Slowing of the pulse* is sometimes erroneously accepted as the criterion It should not be since slowing of the pulse does not always occur in the therapeutic stage and since slowing of the pulse is not attained by digitalis in certain types of myocardial insufficiency Thus Edens ([87]) states that slowing does not occur when hyperthyroidism is present in acute myocarditis in idiopathic hypertrophy or in the small heart of tuberculous diathesis In such conditions the toxic manifestations appear before slowing occurs

When the patient is closely followed the therapeutic stage is often accompanied by the first toxic manifestations which are usually readily recognized The following should be closely observed (1) the urinary output in relation to the intake since diuresis usually characterizes the therapeutic stage and oliguria the toxic stage of digitalis (2) the outline of the heart (3) the character of the heart beat and heart sounds (4) the symptomatic condition of the patient with respect to dyspnea cyanosis and edema (5) the effect on blood pressure and on the character of the pulse and (6) the effect on cardiac function as revealed in electrocardiograms the inversion of the T wave occurs in the therapeutic stage but block and other arrythmias indicate toxicity

The time element in digitalis therapy is important It is unusual to get digitalis effects from any preparation given by mouth in the ordinary dosage in less than 36 to 48 hours more frequently 48 to 72 hours Digitalis given today does not manifest its action until the day after tomorrow Where immediate effect is necessary recourse may be had to strophanthin and where the need is less urgent Eggleston s dosage may be employed provided the ca e is otherwise suitable

Digitalis is cumulative in its effects and consequently should be given in courses When the desired amount is prescribed the digitalis should be stopped and the effect noted The toxic effects are nausea and vomiting vertigo syncope and diminished urinary secretion The pulse may become either slow (vagus effect) or fast (increased muscle irritability) Irregularities may develop a bigeminal or trigeminal pulse is rather pathognomonic of the toxic state Auricular fibrillation may develop Sudden cumulative effects are said to occur but the more closely a patient is watched the less sudden as a rule are the toxic effects of digitalis Nausea and vomiting which herald toxic action often go unheeded

The effect on blood pressure is deserving of comment since digitalis in animal experiments leads to increase in blood pressure Little or no influence on blood pressure is seen clinically In some cases a rise is encountered but more frequently a gradual fall in pressure is seen which is often synchronous with unquestionable clinical improvement Naturally rest diet purgation and depletion also play a role in determining the effect on blood pressure

Substitutes for Digitalis—For routine use no drug can replace digitalis Strophanthin however is unquestionably the best substitute and in certain conditions it is preferable Strophanthin is the most valuable preparation the tincture of strophanthus comparing in no way with the tincture of digitalis

Strophanthin is given in 0 25 to 0 5 mgm doses intravenously and in 0 25 to 1 mgm doses intramu cularly Local massage for 15 minutes at the point of injection obviates the local irritant effect otherwise encountered When used in 1 mgm doses it cannot be repeated within 24 hours a dose of 0 5 mgm may be repeated in 12 hours although in the majority of cases it is unnecessary Doses of 0 25 mgm should be repeated in 8 to 12 hours Strophanthin is given as is digitalis in courses of 2 to 3 days duration

Warning is necessary concerning its use where digitalis has been already administered As already stated digitalis requires 24 to 36 hours to demonstrate its effect The addition of 0 5 mgm strophanthin at the end of a course of digitalis may precipitate alarming toxic mani

festations On the other hand strophanthin is admirable when used in the beginning of a course of digitalis as follows a patient suffering from acute dilatation of the right heart may be bled 0 5 mgm strophanthin given intramuscularly and then a course of digitalis started in the ordinary way From this procedure an almost immediate digitalis effect is secured and maintained

Strophanthin acts pharmacologically and therapeutically much as digitalis but has somewhat less effect in vasoconstriction It constricts the splanchnic terminals as does digitalis but not the vessels of the extremities and cerebrum which may even undergo slight dilatation at times Considerable controversy has been waged over its effect upon the coronaries Digitalis constricts the coronaries and therefore decreases the blood supply to the heart muscle Loeb claims that strophanthin here exerts a dilating influence Voegtlin and Macht using arterial rings find a constricting influence for digitalis and a dilating effect for strophanthin The chief effect of both drugs is identical however in shifting the blood from the venous to the arterial side of the vascular system

The time necessary for the manifestation of their physiological effect is the chief point of difference The strophanthin effect is almost immediate whereas digitalis requires 24 to 36 hours Strophanthin is therefore used in preference to digitalis where the need is urgent

Caffeine or some member of the caffeine group is sometimes substituted for digitalis where the latter fails When slowing results from its use the pharmacological effect resembles that of digitalis However the pulse rate is more frequently accelerated than retarded Unfortunately its use is commonly attended with the development of palpitation insomnia and sometimes nausea vomiting and delirium These untoward effects often appear as early as the effect on the heart consequently caffeine is seldom employed in this connection

But these purin derivatives are excellent diuretics According to Schroeder they exert a specific effect on the cells of the renal tubules and consequently they are often employed in myocardial insufficiency not as a substitute for digitalis but as a synergist from the point of view of renal secretion Theobromine has a more constant renal effect than caffeine and is frequently used in 0 7 to 0 5 gm t i d or in the form of sodio-salicylate of theobromine 1 gm t i d The most valuable preparation of the caffeine group however is theocin which is administered in 0 2 gm (3 grain) doses three times a day for one day It exerts less cerebral effect and consequently does not result so frequently in insomnia It can be repeated on alternate days if its effect disappears rapidly Where the diuretic effect of digitalis is lacking our own prac

tice is to turn to theocin which is given in addition to digitalis and in the manner just indicated

Certain other remedies sometimes substituted are perhaps worthy of mention Squill is of value at times It has a very mild digitalis effect and is an excellent diuretic It is given as the tincture (0 3 to 1 c c) or as the syrup (2 to 4 c c) Neimeyer s or Addison s pills which contain one grain each of calomel digitalis and squill is a valuable preparation Apocynum as the fluid extract (1 c c) convallarin as the tincture (0 3 to 1 c c) and adonidin 10 to 20 mgm are occasionally used but are of very doubtful therapeutic value Spartein sulphate 0 065 to 0 13 gm is rarely employed Cactus grandiflorus is absolutely inert and should be deleted from the pharmacopeia

Adjuncts to Digitalis Therapy —Anemia is not at all infrequent in myocardial insufficiency Iron and arsenic are here of the greatest value Strychnia is occasionally of value Alcohol in small doses for its psychical effect is employed at times in those accustomed to its use when craving is great

The value of charts quickly conveying the effect or need of treatment from the standpoint of the kidney is worthy of emphasis At a glance one accustomed to their use grasps the condition of renal activity

The Symptomatic Treatment of Myocardial Insufficiency

At times certain symptoms become so pronounced as to call for special treatment in addition to the general treatment described above

(1) *Edema* is usually controlled by rest diet restriction of fluids and salts and by digitalis alone or together with one of the caffeine bodies Where these fail or where the anasarca is extreme so that pressure interferes with the action of the heart or lungs tapping of the cavities concerned is necessary Where edema of the extremities is so severe as to threaten gangrene drainage may be employed with success

(2) *Dyspnea* —The cause of the dyspnea should be determined If mechanical paracentesis may be indicated or special attention to diet if there is pressure from intestines filled with gas The back rest may bring great relief For orthopnea morphine 10 mgm and atropine 0 5 mgm often brings relief When these fail and when marked dilatation of the right heart is found venesection and strophanthin answer best

Formerly nitrites were much used in dyspnea associated with hypertension The dyspnea is now considered as evidence of beginning myocardial weakness and calls for digitalis and not for vasodilators

(3) *Arrhythmias* —Digitalis has a marked effect on rhythm This

must be constantly in mind since many arrhythmias encountered clinically are of digitalis origin and the treatment consists in the removal not in the administration of the drug

Auricular fibrillation is the condition in which digitalis produces its most brilliant effects The overstretched auricular muscles are unable to make concerted contractions and instead enter into a state of tremulation or fibrillation These irregular impulses are transmitted to the ventricle producing a confusion of rhythm or absolute irregularity The output of the heart is markedly decreased and its efforts ineffective The main effect of digitalis is lessened conductivity but an influence is also exerted on the irritability of the muscle Improvement in rhythm is often accompanied by prompt and decided increase in blood flow

Digitalis is indicated in auricular flutter Fibrillation is frequently induced which disappears on the removal of digitalis leaving a normal rhythm in its stead Partial heart block is exaggerated by digitalis which intensifies the degree of the block and tends to result in a complete block Unless digitalis is needed for other reasons it should be withheld Atropine on the other hand may be effective in the removal of this form of block Since in complete heart block interference with conductivity is sufficiently complete to effect total dissociation in auricular and ventricular rhythm digitalis can do no harm It renders ventricular contraction more effective and tends somewhat to decrease its rate and consequently is of value Extra systoles are the result of increased myocardial irritability and hence tend to be increased rather than decreased by the drug Digitalis if indicated can be used effectively despite their existence Extra systoles should be treated by general hygienic measures Sinus arrhythmia likewise is exaggerated by digitalis because of the stimulation of the vagus

(4) *Hypertension* —This is best met through general measures such as rest sleep diet and depletion The medicinal lowering of blood pressure is best effected through the use of digitalis Other vasodilators and blood pressure lowering drugs are rarely indicated The use of nitrites should be restricted to conditions in which there is localized arteriosclerosis or arterial spasm in a vital part as in angina pectoris and to cases in which as a result of high blood pressure a vascular accident such as apoplexy is feared It must be admitted however that nitrites occasionally result in benefit when used in conjunction with digitalis and when digitalis along with general measures have failed If used at all the onset and duration of their action should be borne in mind The results of Wallace and Ringer ([44]) in relation to these desiderata are shown in the following tables

Drug	Dose	Time of beginning action	Time of max effect	Duration of action (min)	Max extent of action	Maximum extent of action (mm Hg)
I						
Amyl nitrite	3 min	1	3	7	15	
Nitroglycerin 1 per cent sol	1 1/2 min	2	8	30	15	In normal subjects
Sodium nitrite	1 gr	10	25	60	14	
Erythrol tetranitrate	1/2 gr	15	32	120 40	16	
II						
Nitroglycerin	1/30 gr	2	8	35	3	In arterio sclerosis
Sodium nitrite	2 gr	15	45	120	53	
Erythrol tetranitrate	2 gr	30	60	180	60	

(5) *Palpitation and Cardiac Distress*—Occasionally the gastro intestinal tract is at fault and its responsibility should be investigated Local treatment may suffice The ice bag is frequently the most potent source of comfort Small blisters and belladonna plasters are of value at times Internally potassium iodide is frequently employed with success Tincture aconite may also help at times

(6) *Gastric Symptoms*—Nausea and vomiting are commonly encountered They frequently yield rapidly to the general treatment already described *Their origin must always be determined* since their appearance after instituting digitalis therapy should suggest the possibility of responsibility of digitalis The treatment may be withdrawal of digitalis Similarly Epsom salts may be responsible

All food should be stopped for 12 hours if nausea and vomiting become extreme and nothing should be allowed by mouth except crushed ice Later milk and lime water are allowed in small amounts Gastric sedatives such as sips of cold effervescing drinks champagne apollinaris water or an ordinary syphon are often of value Bismuth 1 to 2 grams creosote 0 1 c c dilute hydrocyanic acid 0 065 c c cocain hydrochloride 5 to 10 mgm or a mixture of tr nux vomica 0 3 c c and soda bicarbonate 0 1 gram may be *tried* *Counter irritation* in the form of a mustard plaster to the abdominal wall is occasionally helpful

Naturally in myocardial insufficiency associated with chronic nephritis nausea and vomiting may be evidences of uremia All of the above methods may be tried without success while some general sedative acting centrally such as chloral 0 3 gram every 4 hours or *morphine* 10 mgm may bring relief Persistent nausea and vomiting particularly if associated with a markedly enlarged and pulsating liver is an extremely serious complication often ending fatally

(7) *Cough*—The cough is usually due to circulatory changes in *the lungs and responds to the cardiac treatment Expectorants are as a* rule contraindicated

(8) *Hemoptysis*—Though most alarming to the patient hemoptysis in myocardial insufficiency is seldom serious The patient should be assured that the hemorrhage is salutary and does away with the necessity of doing a venesection Assurance absolute quiet and an ice bag over the chest usually suffice When the patient is markedly upset a small dose of morphia is often desirable

(9) *Edema of the Lungs*—This is an extremely serious complication and calls for quick action The patient should be bled 400 to 600 c c Morphia 15 mgm should be given hypodermically Atropin 0 5 mgm is used at times but morphine is of greater value

(10) *Insomnia*—This is frequently a very troublesome symptom *A good back rest with side supports often allows a comfortable sleep in* a sitting posture Any of the following hypnotics or sedatives can be tried—paraldehyde 2 to 8 c c in capsules sulphonal 0 6 to 2 gms Hoffman s anodyne 2 to 4 c c spts of chloroform 0 3 to 0 6 c c spts of camphor 1 to 3 c c alone or 2 c c in combination with ether 2 c c veronal 0 3 gm barbital or barbital sodium 0 6 to 1 gm or urethane 1 to 2 gm Where these do not give relief it is better not to waste valuable time Morphia 10 to 15 mgm alone or in combination with atropine 0 5 mgm should be given hypodermically

In these various ways conditions arising from myocardial insufficiency are met The means used are successful in so far as they influence function They can have little if any effect on structure They do in many cases so modify function that discomfort is converted into comfort *dangerous crises averted and life prolonged with a reasonable degree of* daily activity

(8) Medical Organization

Specialization more than any other single factor serves to advance a science A coterie of workers devoting whole time to the advancement of a subject brings to it that concerted continuous thought and effort so necessary for success The field of pharmacology is being tilled and cultivated by an ever increasing group Chairs of pharmacology assure the development of this subject Similarly institutions such as the Speyer House and the Rockefeller Institute and Hospital have contributed greatly to progress The methods adopted by Ehrlich Flexner and Cole in relation to trypanosomiasis syphilis relapsing fever meningitis poliomyelitis *and pneumonia are those most needed in medicine* Cole and his co workers have exercised the type of critical judgment and

employed the numerous controls so necessary for sound progress yet so uniformly lacking in most therapeutic investigation

Pharmacological societies and publications the natural outcome of the development of the science in turn have played a great role in its further development

What is Needed for the Advance of Therapy

Since doctrines control therapy treatment will improve as medicine advances This involves the adaptation to medicine of all that is applicable in science All progress in the fundamental branches eventually advances practice The healing art must give place to the healing science

Sound training in the fundamental sciences in medicine and in pharmacology constitutes the therapeutist s greatest asset The doctor must feel the responsibility of treatment as well as of diagnosis The same thought and individual effort accorded diagnosis must also be accorded treatment Individualistic diagnosis must not be followed by book treatment Common sense individualized and not book authority is needed in treatment

Pharmacology is young Science like history is built by individuals Individual effort in research is the basis of progress in pharmacology Dosage must be reduced to a matter of certainty In the absence of chemical entities standardization of drugs and units are greatly needed otherwise accuracy of dosage is impossible Treatment should always be conducted after the manner of a scientific investigation The remedy and dosage once decided throughout treatment careful observations must be made with adequate record of results Daily notations keeping in mind the disease and the treatment markedly increase the physician s capacity as a therapeutist Graphic methods of record such as electrocardiograms and fluid balance charts are most desirable

Leadership on the part of leaders of medicine is needed Therapeutic nihilism or failure to utilize useful remedial measures on the part of teachers of medicine engenders neglect of therapy in the mind of the student Organized effort is necessary to combat the growing evils of advertising on the part of proprietary pharmaceutical interests The physician must see to it that treatment rests on the basis of science and not on the claims of drug houses

It is interesting to note that progress in therapy has been associated with a marked decrease in the number of drugs used The application of science has revealed true values as a result of which the majority of drugs have fallen into disuse There is however great room for

further progress along such lines New drugs are needed but for each one adopted many should be discarded

The complexity of the human organism of life processes and to a less extent of drugs demands breadth and depth in investigation the details of which are usually beyond one individual Group investigation is as greatly needed as group practice In chemotherapy chemistry and experimental medicine are represented but chemical detail is usually best handled by chemists and therapeutic detail by physicians Each deserves the best individual effort of a specialist The master mind must deal with the fundamental conception and with close scrutiny of all details rather than with their actual execution This involves organization and great expenditure of time In America one of the greatest needs of modern medicine is a national institute for pharmacological research

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CHAPTER XXIII

EDEMA

By GEORGE D BARNETT

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HISTORICAL

Dropsy has been an outstanding problem since the beginnings of medicine It is mentioned in the Ebers papyrus and on the clay tablets of medical prescriptions of ancient Assyria Modern nutritionists have noted with satisfaction the report that 2 300 years ago Heraclitus disgusted with mankind retired to the mountains lived on vegetables and herbs alone acquired dropsy and died The Hippocratic writers have a good deal to say about it classifying it regarding it as a liquefaction of the tissues brought about by some malady of the spleen and treating it by laxatives and by abdominal puncture when there was much ascites Others among the ancients thought dropsy due to a disorder of the liver as often it doubtless was Saliceto in 1275 mentioned an association with scanty urine and hardened kidneys but otherwise the medieval writings are not enlightening Even Sydenham who gives so vivid a description of cardiac edema does not mention a suspicion that the heart might be at fault In the XVIII Century Morgagni found valvular defects in many cases of dropsy but did not carry the

matter farther Withering knew no distinction between cardiac and renal dropsy and was disappointed that cerebral and ovarian dropsies did not yield to the fox glove Not until two hundred years after Harvey was edema recognized as a symptom common to many disease pictures, and this we owe to Corvisart, to Laennec and especially, to Bright

A *rational consideration of the mechanism of dropsy* also began early in the last century, when the rise of clinical physiology brought numerous suggestions, such as the lymphatic obstruction hypothesis of Broussais, the increased capillary filtration of the Ludwig school and Heidenhain's idea of augmented lymph secre tion Present concepts date from 1896 when Starling[31] first pointed out clearly that a balance between hydrostatic and osmotic forces determines fluid move ment through the capillary walls and is, consequently, concerned primarily in edema formation For fifty years the hypothesis has served those who have wished to understand edemas There have been some clinical discrepancies and the recent studies of electrolyte and water balance[10, 17] have made it plain at least that we have not arrived yet at a complete knowledge of the physiology of edema A brief consideration of some of the factors that influence fluid distribu tion in the body will permit an understanding of some of the mechanisms con cerned

The Physiology of Fluid Distribution

Edema is a local or general increase in the interstitial fluid of the body Normally the interstitial compartment is separated from the blood plasma by the capillary endothelium, a membrane through which water and crystalloid sub stances pass with ease, but which is largely impermeable to colloids chiefly the proteins of the plasma It is separated from the intracellular fluid by the cell walls, which are permeable to water but not freely so to electrolytes to proteins or to most other solutes Membrane permeabilities within the body probably are never absolute, normal interstitial fluid probably contains a small amount of protein[33] and the conditions under which variations in permeability may occur frequently are not understood The interstitial fluid constitutes the im mediate internal environment of the body cells, and its volume and the total os molar content of its dissolved substances are maintained at quite constant levels by gain or loss of fluid from or to the vascular or cellular compartments and in directly, by excretion or retention of water or solutes by the kidneys[10, 17]

Fluid transfer through the capillary walls is of especial importance in the edema problem Normally the effective hydrostatic pressure which maintains a constant flow from capillaries to tissue spaces is the capillary pressure minus the tissue pressure and the effective osmotic pressure which moves fluid in the op posite direction is the osmotic pressure of the plasma colloids chiefly proteins,

minus the osmotic pressure of the proteins in the tissue fluids.* For further discussion and diagrams see Vol. III, Chapter X of Oxford Medicine.

The Starling Equilibrium

It was this balance of hydrostatic against osmotic forces that Starling postulated in 1896, and its validity as the immediate mechanism by which fluids are moved through membranes in the body is beyond question. Landis[1] has shown that the actual measured pressures conform to the hypothesis. Schade[2] has demonstrated the mechanism in a laboratory model, and Peters[3] reminds us that the fact that extracellular fluid has been shown to have the composition of an ultrafiltrate of plasma is even more substantial proof of its validity. Apparent discrepancies are recorded occasionally in the literature, but no data are given which include measurements of the effective hydrostatic and osmotic pressures.

Possible Changes That Favor Edema Production

There are many possible changes in the Starling equilibrium in the direction of edema production. If the flow of lymph from a region be obstructed, the increasing tissue pressure will decrease the outward flow from the capillaries until it equals the return flow inward, and during this period edema fluid will accumulate. Decrease in the effective colloid osmotic pressure may result from diminished plasma protein concentration or from increased protein in the tissue fluids, due almost always to increased permeability of the capillary endothelium. Hypoproteinemia has many possible causes, which Rytand[4] has outlined (Table I).

TABLE I

PHYSIOLOGICAL CAUSES OF HYPOPROTEINEMIA

A. Loss and destruction of body protein
- I. Urine (Bright's disease)
- II. Ascitic fluid (cirrhosis with paracenteses)
- III. Tissue (cachexia)
- IV. Fetus (pregnancy)

* The effects of hydrostatic pressure are obvious. The nature of the osmotic action is perhaps clarified by noting that the protein molecules within the capillary by their mere presence and because they cannot escape obstruct the outward diffusion of water and dissolved crystalloids, but in the fluid of the tissue spaces there is nothing to obstruct their diffusion inward. The net flow due to the plasma proteins is, therefore, inward. By this concept the osmotic force which moves fluid is derived from the universal kinetic energy of molecular movement and need not be regarded as a mysterious attractive or drawing force exerted upon water molecules by dissolved substances. By another similar concept the net diffusion of water and crystalloid molecules is inward because they are in higher concentration outside than inside the capillary.

B Retarded formation of serum protein
  I Lack of dietary protein
    (a) Absolute total dietary insufficiency
      (1) Starvation
      (2) Pyloric obstruction
      (3) Diarrhea
    (b) Relative total dietary insufficiency
      (1) Pregnancy
      (2) Hyperthyroidism
      (3) Diabetes mellitus
    (c) Dietary protein deficiency
      (1) Low protein diet
      (2) Pancreatic disease

  II Altered states of the body
    (a) Normal
      (1) The newborn
    (b) Abnormal
      (1) Hepatic disease
      (2) Bright s disease
      (3) Beriberi

  III Unexplained

Increased capillary permeability may result from the damaging effect of a local or general toxic agent, and capillary dilatation from any cause probably produces some degree of protein leak So a rise in tissue temperature from the application of heat from fever or even from hot weather may increase tissue fluids Nervous impulses, normal or abnormal, also may increase capillary permeability both by simple vasodilatation and probably also by a neurochemical mechanism

Increase in the effective capillary hydrostatic pressure may occur if there is obstruction ahead in the veins, or because of increased capillary volume if there is arteriolar dilatation or increased total plasma volume Less obvious are the effects of electrolytes, especially sodium salts, which may have a profound effect on water distribution in the body[10]

Salt Effects

Physiological variations in the volumes of the three fluid compartments (vascular, interstitial intracellular) are not normally very great Fluid usually enters the blood stream from the gastrointestinal tract Selective absorption of water and salts in the intestinal villi and prompt renal excretion of excesses of one or the other combine to make the electrolyte concentration changes in the plasma minimal Whatever added volume of fluid remains in the plasma increases the

hydrostatic pressure and decreases the colloid osmotic pressure in some degree and both of these changes lead to increased outflow from capillaries to interstitial fluid. Thus salt solution retained for even a short time is distributed rapidly throughout the extracellular compartment. Large amounts will increase any edema already present or the process may combine with pathological factors to produce an initial clinical edema. Sufficiently vigorous and prolonged administration of salt and water may even cause slight edema in normal subjects. If experimentally or as a result of pathological conditions the interstitial fluid becomes hypertonic there will be an osmotic flow of water into it from the intracellular fluid and conversely, if interstitial fluid becomes hypotonic its volume will shrink by osmotic transfer of water into the cells. The occurrence of such a loss of edema without change in weight of the patient has been described.

It should be noted here especially that the transfer of salt solution from plasma to tissue spaces is to be regarded as a simple consequence of the shift in the Starling equilibrium acting throughout the vast capillary membrane and that it implies no peculiar ability of the tissues to attract or to retain salt. Flow of fluid in the opposite direction also occurs with equal ease whenever the balance shifts to require it. This usually involves renal excretion of salt and water with reduction in plasma volume and capillary hydrostatic pressure and increase in plasma colloid osmotic pressure. The kidney can excrete excess salt or excess water as the occasion demands and slight hypotonicity or hypertonicity probably can be an adequate stimulus but beyond this the conditions under which body fluid volumes are regulated and how they are regulated by the kidneys is not understood completely. Some of the factors involved are the volume of blood flow to the kidneys, the number of active glomeruli and the acceptance or rejection of water or electrolytes by the tubule cells.[90] It is here that certain of the hormones are active.

Hormone Effects

An antidiuretic substance is elaborated by the pituicytes of the neurohypophysis and may be identical with the pressor hormone pitressin. It controls effectively the polyuria of diabetes insipidus and participates in the normal fluid balance. The steroid hormones of the adrenals and gonads are concerned also with electrolyte and water balance[20] and thus indirectly with the edema problem. In Addison's disease deficiency of the adrenal cortical hormone leads to a low level of the sodium salts in the plasma, to dehydration, to low plasma volume and to shock. Replacement therapy with cortical extract or desoxycorticosterone may then so increase the salt and water content of the extracellular fluid that general edema results. The action of the adrenal cortical hormone is upon the renal tubules promoting reabsorption of sodium salts. Most of the hormones

of the ovary and testis are said to promote retention of water and sodium salts[36] but their mode of action has not been established Lack of thyroid hormone brings about in some manner an increase in soluble colloid material probably mucoprotein, in the interstitial fluid The effective colloid osmotic pressure of the plasma is reduced and edema results Fluid retention is seen also at times during insulin therapy rarely with slight but definite edema, especially in patients recovering from coma Excessive infusions of salt solution as well as some lowering of the plasma proteins from a dietary cause not related to insulin are responsible frequently A true hormonal action here is doubtful

Compensation for Varying Capillary Pressure

Hydrostatic pressure in the capillaries varies widely in different parts of the body In the standing position gravity increases the pressure greatly in the legs, and pressures are believed to be low in the capillaries of the lungs and of the liver *Since the colloid osmotic pressure of the plasma is presumably* about the same throughout the circulation, the question must arise as to how a balance can be obtained Partial answers are available In the liver a high protein content of the tissue fluid lowers the effective colloid osmotic pressure and is evidenced by high protein figures in liver lymph[37] It has been suggested that this is protein newly formed in the liver In the lower extremities lymph flow is greater, indicating that outflow from the capillaries is maintained there at a higher level Local increase in capillary permeability is another possible adjustment to offset low capillary hydrostatic pressure but good *evidence of* such a compensation is lacking It is of some teleological interest to note that in the lungs the low capillary pressure is strikingly adapted to the maintenance of dryness in the alveoli

Imbibition of water by the colloids of the tissue cells under the influence of environmental changes has been considered important in edema formation, but edema fluid is essentially interstitial, and the chief known changes that take place in intracellular fluid volume are osmotic, the result of differences in concentrations of electrolytes inside and outside the cells *The contribution* of colloid imbibition to edema is small and the occasions of its participation are not known

Clinical Edemas

Edema is nearly always a pathological finding although occasionally small local accumulations of excess tissue fluid may be recognizable in normal individuals A transient slight swelling of the eyelids and periorbital tissues may be present in some persons on arising in the morning and others *may* show a slight edema of the ankles on prolonged quiet standing

The interstitial space is very distensible and weight curves in certain patients show that it can accept as much as eight or ten liters before edema appears Bedside recognition of minimal edema is occasionally uncertain and opinions may differ in a given case The phenomenon of pitting by which we commonly demonstrate subcutaneous edema is merely the displacement of freely movable fluid in the intercommunicating tissue spaces but sufficient pressure maintained sufficiently long will produce pitting in the normal subject and the borderline between normal and pathological pitting thus is not sharp Edema that has been present a long time is apt to become hard and to pit with difficulty This is said to be due to connective tissue proliferation In myxedema there is said to be a nonpitting edema but if the fluid resides in the intercellular spaces and not in the tissue cells the term is without meaning True non pitting edema other than the weight increase usually called pre edema probably is non existent

The Edema of Circulatory Failure

Cardiac edema usually is a late manifestation of heart failure Frequently it is noticed first as a slight swelling above the shoetops present in the evening and gone the next morning and examination at this time will show distention of the neck veins which also disappears promptly with rest Often preceding this edema there has been a long period of increased load upon the left ventricle such as hypertension aortic valve disease with gradual asymptomatic hypertrophy and dilatation later dyspnea and with physical findings due to pulmonary congestion or frank pulmonary edema This common clinical sequence from the left ventricle through the lungs to the systemic veins strongly supports the backward failure hypothesis of cardiac insufficiency with its corollary that the edema of heart failure is due immediately to the increased intracapillary pressure which must follow venous congestion Starling proposed this mechanism[37] and many investigations have served to confirm it Landis and others [1] have shown that even a small rise in venous pressure is sufficient to cause measurable amounts of fluid to accumulate in the tissues and recently Landis and associates[17] have reported that after experimental cardiac damage of several kinds in dogs exercise produces elevation of venous pressure whereas in normal dogs it is reduced by similar exercise It seems proven therefore that a chief immediate cause of the edema of congestive heart failure is increased hydrostatic pressure in the capillaries and that the effective increase is at first that which occurs during exercise

Some decrease in plasma proteins is not an uncommon finding in heart failure and is the sum of several items[15] The diet is often low in protein and with severe congestion loss in the urine may be considerable Late in heart failure there is usually a significant increase in blood volume[27] in which both hydremia and increased permeability due to anoxia may contribute to the lowered plasma pro

tein percentage and finally the congested liver may be unable to produce new protein at an adequate rate. Although the plasma protein levels are never very low, any decrease will contribute to the accumulation of edema fluid.

Increased permeability of the capillary walls as a result of anoxia is mentioned often as a factor in cardiac edema. Landis has demonstrated that lack of oxygen will make the endothelium more permeable, but the degree of anoxia in his experiments is greater than that usually found in any but terminal stages of heart failure. A necessary result of increased permeability would be a high concentration of protein in the edema fluid. Reported values vary considerably but do not indicate any significant leakage of protein. The protein concentrations found in cardiac edema fluids also do not show any correlation with the duration of the edema. So it must be concluded that the integrity of the capillary wall is rarely much impaired.

Increase in the sodium salt content of the body will bring about an increase in extracellular fluid volume in cardiac patients as well as in normals and thus will promote edema formation. With failure of the circulation there may be a marked reduction in blood flow to the kidneys[38] with impaired excretion of sodium salts and water. This would increase an edema already present, but that such a mechanism is ever active early in the course of heart failure is unlikely.

Hydrothorax of some degree is almost a constant part of the edema of late heart failure. Its appearance earlier and more extensively on the right side is an old clinical observation which has had several explanations such as the pressure of the enlarging heart on the right pulmonary vein or stasis in the azygos vein. Dock believes that like other cardiac edema it is localized by gravity, as there is a longer return course of blood from the right lung than from the left. Right lateral decubitus thus will favor its accumulation.

Pulmonary Edema

Intracapillary pressure is considerably lower in the lung than in the systemic circulation and the Starling balance thus should be displaced in favor of dryness in the alveoli. The ability of the pulmonary capillaries to absorb fluid from the air cells is in fact extraordinary. Drinker[12] cites the experiment of Colin, who in 1873 poured 21 liters of water into the trachea of a horse in a period of 3½ hours without ill effect.

Acute pulmonary edema[1, 24] occurs commonly in patients with heart failure. Its association with long standing overwork of the left ventricle is so striking that the conclusion seems justified that left ventricular failure with increased pressure throughout the pulmonary circulation is an important mechanism in its production. Welch[41] suggested such an explanation in 1878 and supported it with animal experimentation, but Wiggers[43] was unable to produce pulmonary

edema in dogs in which very high capillary pressures were maintained for thirty minutes and believes that back pressure alone rarely can account for acute pulmonary edema in man The frequent occurrence of attacks of acute pulmonary edema during the night when left ventricular recuperation should be greatest has been an enigma Acute myocardial strain from disturbing dreams has been suggested but a more likely cause is a nocturnal increase in blood volume in the lung as a result of rest[m] Systemic venous congestion is relieved and reabsorption of tissue fluid may occur The bout of dyspnea which often begins the attack also may favor transudation by lowering intrathoracic pressure

Other factors may be active also in the production of acute pulmonary edema Drinker believes that increase in capillary permeability may have even greater influence than pressure changes The lung capillaries are particularly sensitive to oxygen lack and since their endothelial cells receive their oxygen from the air any interference with the air supply may initiate local or general pulmonary edema Alveolar transudation then further decreases the oxygen supply and a vicious cycle becomes active endothelial anoxia — transudation — increased anoxia

Nervous influences are active also The nervous mechanism may be excited directly as in the pulmonary edema which occasionally accompanies skull fracture or encephalitis or reflexly as in the albuminous expectoration of paracentesis The frequent brilliant therapeutic effect of morphine in acute pulmonary edema is to be ascribed to the sedation of nervous impulses The mode of action of neurogenic influences is unknown but a local pulmonary neurochemical mechanism has been suggested

The edema produced by inflammation or by irritant gases presumably is identical with the edema of inflammation elsewhere

It is evident that a variety of elements may contribute to produce alveolar transudation in the lungs and that clinically the situation may be complex and not subject to exact analysis

The Edemas of Nephritis

The edema of acute nephritis usually is slight and may escape notice altogether A little puffiness about the eyes and of the face is common and there may be a small amount of subcutaneous edema elsewhere Widespread edema has been reported rarely but many such cases may include edema from an early nephrotic stage or from the heart failure which is seen occasionally in acute nephritis Exact determination of the cause of the edema is sometimes difficult

The nature of the edema of acute nephritis is in some doubt That there is widespread vascular damage is plain from the occurrence of hematuria and of retinal hemorrhages and it is evident that the capillary wall must have lost in

some degree its efficiency is a membrane semipermeable to the plasma colloids Edema fluid resulting from such a breakdown would have of necessity a high protein content and here the reported figures are not in agreement However it will be noted that the figures of Warren and Stead[37] for acute nephritis are higher than they found in the edema fluid of heart failure and considerably higher than those reported for the edema of nephrosis Capillary damage is, therefore probably a principal part of the mechanism

The most striking edema of renal disease is the widespread and persistent edema characteristic of the active (subacute) or nephrotic stage of glomerulonephritis and in the other nephroses with high albuminuria It is of interest that Bostock[4], a chemist who worked on Bright's edematous patients reported I think I may venture to say that the serum generally in these cases contained less albumin than in health, although I am not able to state precisely the amount of the difference" Clinicians long believed that loss of protein in the urine led to a watery condition of the blood which favored transudation and not until Epstein s valuable contribution in 1917 were the Starling concepts used to explain this edema Epstein[16] pointed out that the plasma proteins depleted by excessive loss of protein through the kidneys were no longer able to bring about the normal return of fluid from the tissue spaces to the blood Clinical observations have confirmed abundantly the correctness of this interpretation and the plasmapheresis experiments of Leiter and of Barker and Kirk have been further elucidating They show that by lowering the plasma protein in dogs a level is reached at which edema occurs with great regularity and the animal recovers completely, when the plasma protein level is restored to the normal range The edema of nephrosis differs somewhat from this experimental edema because the protein lost in the urine is principally albumin instead of the mixed albumin and globulin of plasma The globulin fraction of the remaining plasma proteins is therefore greater than normal Globulin molecules are large and exert less osmotic pressure gram for gram than do molecules of albumin, so the level of total plasma protein at which edema may occur, is a variable one and will depend on the albumin globulin ratio There is also at times a lack of correlation between the amount of protein losses and the plasma protein level In some patients the plasma protein concentration may be low after relatively small losses in the urine while in others large losses may cause only slight lowering of plasma levels Variations in the ability to replenish plasma proteins seems probable

Spontaneous disappearance of the edema may take place, while the plasma proteins are still low and such findings are cited to discredit the Starling hypothesis These discordant data however never include measurements of effective osmotic or hydrostatic pressures Furthermore it should be remembered that in the nephrotic edemas the Starling equilibrium may be operative at a low level

Low colloid osmotic pressure because of low plasma protein is balanced by low hydrostatic pressure because of increased tissue pressure Loss of edema may well begin in response to slight lowering of the hydrostatic pressure at very low levels of plasma protein Even slight diuresis the mechanisms for which are not clearly understood might be an initiating factor Warren Merrill and Stead[39] point out that the increased tissue pressure due to edema is an important factor in determining the size of the plasma volume in patients with low plasma protein levels The decrease in colloid osmotic pressure of the plasma is compensated for by the increase in tissue pressure usually permitting the patient to maintain an adequate blood volume

Finally in nephritis we may have the edema of heart failure including acute pulmonary edema as a part of the clinical picture This is seen most often late in the disease when heart failure results from the long standing hypertension When heart failure supervenes during or closely following the active stage of a glomerulonephritis clinical distinction between renal and cardiac responsibility for the edema may be impossible

In the treatment of nephrotic edema restriction of salt may be of value but the results are often unsatisfactory and erratic[6] Attempts to raise the plasma protein level by a high protein diet are also disappointing and by increasing the work of the kidney may be harmful On the other hand diets too low in protein may add more edema to the picture The use of human plasma albumin[34] intravenously may be effective when available but large amounts are necessary retention of about 75 grams of albumin being required to bring about an increase of one per cent in the plasma protein level and with continuing albuminuria a lasting effect cannot be expected The substitution of other colloids has been practiced extensively, such as acacia or pectin While they are effective in reducing the edema they are known to diminish protein formation in the experimental animal and their ultimate fate in the body may entail other disadvantages[2] Their hazards appear to outweigh their usefulness With a low salt diet water need not be restricted and may have some diuretic action Other diuretics such as the purines and the organic mercurials are used often, but opinion is divided as to their harmfulness in the presence of kidney disease For the relief of stubborn extreme edema Southey tubes may be used and serous transudates when large likewise are best removed by paracentesis

Nutritional Edema

In many states of malnutrition considerable edema may be seen Lack of vitamins in the diet a low protein ration failure to absorb or to utilize vitamins and proteins because of bowel disease are common etiological pictures Liver function often is below normal with impaired protein formation and low plasma

protein levels In the United States during the depression years many cases of beriberi with edema were seen identifiable chiefly by the history of inadequate diets, the presence of peripheral neuritis and of greatly dilated hearts which re turned to normal size promptly under vitamin B_1 therapy The edema in these patients is largely that of heart failure, but some reduction of plasma albumin is common, and in some instances vasomotor paresis may augment intracapillary pressure The starvation edemas seen so abundantly in prison and concentra tion camps form a striking and appalling group Lack of adequate protein intake and eventually the utilization of amino acids for body fuel instead of protein synthesis combine to produce low plasma levels of protein An accompanying anemia may contribute to the edema by increasing capillary permeability

Whether the edema and ascites of Laennec's cirrhosis belong in the nutritional group is not fully settled The toxic agent responsible for the hepatitis is un known but a dietary factor is suspected Portal obstruction alone does not produce ascites in experimental animals and probably not in man A low plasma protein level is a constant finding in the stage of ascites and is the result of im paired protein formation in the damaged liver and later the result of the loss of protein into the ascitic fluid Usually the albumin globulin ratio is diminished or reversed, and while edema levels are not reached the loss of plasma colloid osmotic pressure plus the increased capillary pressure from portal obstruction will account adequately for the ascites as well as the leg edema Partial obstruction of the vena cava by the ascites is often mentioned as a factor, but evidence of obstruction of the venous return from the legs usually is lacking Treatment of the edema and ascites of portal cirrhosis with diuretics is unsatisfactory and treatment directed toward the relief of the underlying liver disease also is dis couraging in cases which have progressed to this stage

Obstructive Edema

Edema resulting from obstruction to veins or lymphatics is common Uni lateral or unequal edemas of the legs are most frequently the result of venous obstruction from thrombosis or varicosities Edema from the pressure of an enlarging uterus or a malignant tumor also is not infrequent Whether or not occlusion of a vein will cause edema depends upon the amount of collateral cir culation available and upon the presence or absence of other factors which might contribute to edema formation In experimental animals edema seldom occurs after ligation of even large veins such as the femoral or the inferior vena cava and in man such edema may be transient disappearing with the development of collateral channels In cachectic individuals even moderate degrees of venous obstruction such as may result from an unusual position in bed may result in edema Here low plasma proteins are a frequent contributing factor In patients

with congestive heart failure venous thrombosis may occur as a result of stasis and local edema due to minor thromboses is seen not infrequently

The edema of lymphatic obstruction has a characteristic appearance There is no redness or cyanosis of the skin and having attained a certain moderate degree, it may remain at that level for long periods This corresponds to the mode of its production Tissue drainage via the lymphatics being stopped, the outflow from the capillaries will equal the return flow into them and there will be no occasion for further increase of tissue fluid In very long standing lymph edema the skin and subcutaneous tissues are apt to show some hypertrophy and induration

There are many conditions in which lymphatic obstruction occurs Lymph angitis may cause temporary or at times permanent obliteration of lymph channels or they may become occluded by invading cancer cells Surgical removal of groups of lymph nodes is followed often by regional edema In tropical elephantiasis the lymphatics are blocked by filaria In addition a good many cryptogenic cases of lymphedema are seen[8] including the rare familial edema of Milroy and a group of somewhat similar sporadic lymphedemas occurring especially in women Some of these are believed to have resulted from old pelvic inflammatory disease[12] The pathogenesis is not known (See also Oxford Medicine Vol II Chapter XIV-C Swellings of the Limbs due to Local Causes)

Inflammatory Toxic and Allergic Edemas

The presence in the tissues of substances toxic to the vascular and tissue cells produces edema regularly as a part of the reaction Burns bites chemical irritants of various sorts are the common exciting agents and a humoral toxic agent probably is active also in tissues that are especially sensitive to allergic antigens and to certain physical agents such as heat cold and mechanical stimulation Common to all of these reactions is an early hyperemia presumably with increased intracapillary pressure and an increased permeability of the capillary wall as evidenced by the high protein content of the edema fluid The cloudy swelling of inflammatory tissue cells is evidence that some increase in the volume of the cells must occur also The edema that may persist after active inflammation has subsided is due to the lowering of tissue pressure which follows stretching of the tissues

Of particular interest is the group of skin reactions with wheal formation that are produced by heat chemical irritants mechanical stroking and probably at times by neurogenic impulses Lewis[23] has presented evidence that a substance resembling histamine is liberated in the skin in response to each of these agents and that the same mechanism is common to the action of all of them In the case of remote response to nerve impulses such as that in herpes zoster and some

urticarial lesions Dale[9] has suggested that liberation of acetylcholine at the arteriolar nerve endings may play a role, producing both vasodilatation and increased capillary permeability There is a large group of cases of asthma, urticaria and angioneurotic edema, in which specific allergy may not be demonstrable, and in which psychic and nervous influences frequently precipitate the attack In these a neurochemical mechanism seems not unlikely The rare local edemas occurring in diseases of the central nervous system probably would belong in the same group

The Clinical Investigation of Edema

The cause of most edemas can be determined by means of a good history and physical examination and a routine urine analysis In the study of cases of obscure edema the following measurements may be of value, (1) total plasma protein concentration, (2) fractionation of plasma albumin and globulin (3) colloidal osmotic pressure of plasma, (4) blood volume (5) blood and urine chlorides (6) hematocrit determination, (7) quantitative protein in the urine, (8) weight curve of patient (9) venous pressures

Fairly satisfactory clinical methods are available for total plasma protein determinations based on the parallelism between protein content and specific gravity[19] Present clinical methods for albumin globulin fractionation are unsatisfactory but may be of some value particularly in determining changes from time to time Colloid osmotic pressure measurements are rarely available clinically and are worth little unless done by special workers Blood volumes usually are determined clinically by convenient dye methods, whose inaccuracies are many and well known[27]

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September 1, 1947

The following pages will be used at a later date

CHAPTER XXIV

THE REGULATION OF BODY WATER AND ELECTROLYTE IN HEALTH AND DISEASE

By DANIEL C. DARROW AND EDWARD L. PRATT

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Without a considerable knowledge of the physiology of body water and electrolyte physicians cannot properly treat dehydration, edema, acidosis, alkalosis and shock, or plan a rational therapy when all or part

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indicate the volumes of water in each kind of fluid The amount of extracellular sodium and intracellular potassium is indicated by the respective areas The amounts of the various electrolytes contained in each compartment are indicated by the concentrations multiplied by the volumes

It will be seen that total water per kilogram of tissue is slightly greater in infants than in adults For the first months of life extracellular water in infants is about 30 per cent of the body weight Although the intracellular water of adults may be slightly less than 45 per cent of the body weight this figure is suitable for all ages Actually the total body water varies appreciably in normal individuals The chief differences are accounted for by variations in the proportions of fat Since fat is deposited with relatively little water fat individuals contain relatively less water per unit of weight However the quantitative relationships between the two types of fluid are essentially the same in normal individuals except for the variations with age

Since the changes in body water and acid base equilibrium are explained chiefly by variations in water sodium potassium and chloride the discussion will emphasize the role of these constituents First the total intracellular sodium is about 7 mM per kilogram and approximately equivalent to total extracellular bicarbonate or one fourth of the total extracellular sodium excluding the sodium of bone salts[3] The sodium in bone salts need not be considered again since this sodium does not alter the sodium available to the rest of the body except when bone salts are being deposited or removed This factor is small in any short period since there is 1 mM of sodium for each 30 mM of calcium in calcified material

Normally intracellular sodium is variable since sodium can be transferred from intracellular to extracellular fluids and vice versa The charts show the usual high normal value for intracellular sodium In normal individuals the variations are chiefly in the direction of lower values Since the transfer between the two phases of body fluid apparently is accomplished without change in extracellular chloride the effect on extracellular fluids is to alter the amount of sodium available to form bicarbonate If total body electrolyte does not change transfer of extracellular sodium to intracellular fluids decreases the concentration of bicarbonate in extracellular fluids and transfer of intracellular sodium to extracellular fluids increases the concentrations of bicarbonate in extracellular fluids Hence the shift of sodium between the

of the fluid requirement must be given parenterally, or electrolyte has been lost in large amounts in sweat, urine and gastrointestinal secretions.

Previous concepts of the physiology of body fluids were dominated by two postulates which are now known to be erroneous. First, cellular membranes were regarded as practically impervious to sodium and potassium and, second, only alterations in extracellular electrolyte were thought to be accessible to fluid therapy. During the past fifteen years analyses of the tissues of experimental animals and determinations of the balances of water and electrolytes in patients have demonstrated that intracellular fluids undergo fairly rapid changes in composition which alter profoundly the acid base equilibrium of extracellular fluids. Furthermore, the changes in composition of intracellular fluids, particularly the loss of potassium, and the alterations in the concentration of electrolytes in body fluid affect the function of cells.

The Relation of Extracellular to Intracellular Electrolyte

In order to enable the physician to visualize the quantitative relationships between extracellular and intracellular electrolyte, a schematic representation of the composition will be presented.[1] The extracellular fluids will be considered to have the composition of an ultrafiltrate of plasma. The intracellular concentrations will be represented as those of rat and cat muscle. Both concentrations will be expressed per kilogram of water. Data are available which indicate that the intracellular compositions of the muscle of young and mature cats are essentially the same and that human muscle has about the same composition as that of other mammals. The intracellular composition of the various tissues is similar to that of skeletal muscle. Some of the changes in intracellular composition which will be described are known not to develop to the same extent in other tissues but similar changes probably take place. Since the intracellular fluid of muscle comprises about 70 per cent of the total intracellular fluids, the errors are not significant in depicting the relationship between extracellular and intracellular fluids for the body as a whole.

Charts I and II illustrate the relationships of extracellular and intracellular fluids of one kilogram of tissue in babies and adults. The extracellular concentration of sodium is represented on the ordinate for extracellular fluids, while the intracellular concentration of potassium is represented on the ordinate for intracellular fluids. The abscissae

electrolyte on the acid base equilibrium and the distribution of body water

Second intracellular potassium in normal animals may be about 10 per cent lower than the values shown on the charts This variation may occur without appreciable alteration in body water or acid base equilibrium The charts show the high normal figure since this is the

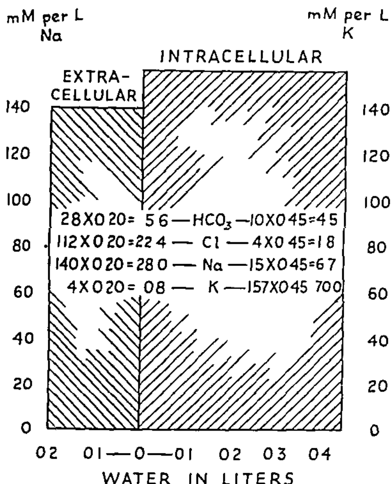


Chart II Diagram of body fluid of 1 kilogram of tissues in adults and children For description see Chart I

two compartments is an important mechanism for diminishing the variations in extracellular bicarbonate In abnormal conditions changes in the distribution of sodium explain the development of disturbances in acid base equilibrium In many clinical situations this mechanism functions in addition to the usually described buffers of the blood and must be considered in the explanation of the effects of balances of

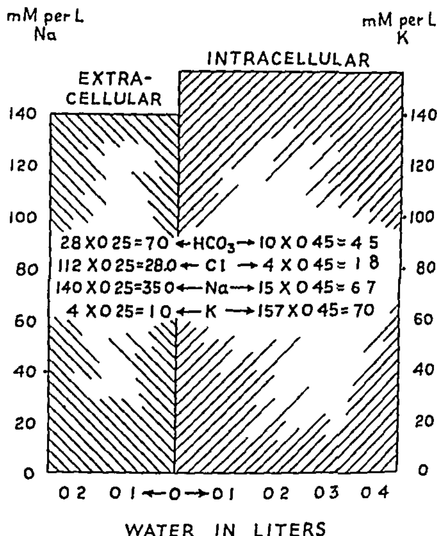


Chart I Diagram of body fluid of 1 kilogram of tissue in infants The concentration of sodium and potassium is represented on the ordinates for the extracellular and intracellular fluid respectively The volumes are represented on the abscissae The total contents are given by the concentration multiplied by the volumes

duce the same changes in both extracellular and intracellular fluids At biological adjustment a deficit of one of these ions leads to deficit of the other Intracellular sodium may reach several times the normal value and several times the equivalence of the bicarbonate of extra cellular fluids This relationship is important first because alkalosis will

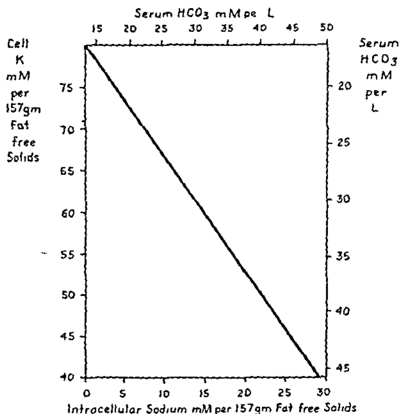


CHART III Relation of the concentration of serum bicarbonate to intracellular sodium and potassium of muscle The line shows the relation of intracellular sodium to potassium the bicarbonate concentrations on the ordinate are the best fit for intracellular potassium while those on the abscissae are the best fit for the intracellular sodium The values for intracellular sodium and potassium are for the same amount of intracellular fluid used for 1 kilogram of tissue in Charts I II and IV

one usually found in rats and cats Changes in intracellular potassium may occur without detectable changes in intracellular sodium, though there usually is a reciprocal relation between intracellular sodium and potassium

Third under abnormal conditions as much as one half of the intra cellular potassium of muscle may be replaced by about two thirds of the equivalent amount of sodium This change in intracellular electrolyte was first discovered in rats subjected to diets low in potassium[4,5] or receiving repeated injections of desoxycorticosterone acetate[6,7] As will be pointed out later this type of deficit of potassium develops as a result of decreased intake of potassium and increased output in urine stools gastrointestinal secretions and sweat Deficit of potassium may result also from processes leading to release of this ion from the cells

Fourth there is a predictable relationship between the acid base equilibrium and the composition of muscle under certain circumstances[2] Chart III shows the relationship between the concentration of bicarbonate in serum and the intracellular sodium and potassium of 157 grams of fat-free muscle solids Since this amount of fat free solids is associated with 450 grams of intracellular water the chart shows the intracellular composition for the same amount of intracellular fluids as charts I and II show for 1 kilogram of tissue The relationship was demonstrated for rats subjected to any one of the following conditions (1) loss of chloride or primary metabolic alkalosis (2) loss of sodium or primary metabolic acidosis and (3) primary deficit of potassium Since water and other ions were abundantly available the chart is based on conditions in which the kidneys would adjust body water and electrolyte to a deficit of only one of the ions sodium potassium or chloride The relationship may be regarded as a biological adjustment or steady state for these conditions The adjustment must be considered a biological one since a chemical equilibrium or steady state would be achieved in several hours and not require several days The chart is useful in illustrating the sort of changes which the body will tend to develop with a deficit of one of these ions when the kidneys are able to maintain a relatively constant composition of the body fluids

The chart is based on data from rats where the relationship is readily demonstrated Clinical studies show that the relationship is manifested in humans In dogs[8] it is difficult to induce alkalosis in response to potassium deficiency though the same changes in cellular composition result from deficit of potassium

It will be seen that deficit of chloride and deficit of potassium pro

duce the same changes in both extracellular and intracellular fluids At biological adjustment a deficit of one of these ions leads to deficit of the other Intracellular sodium may reach several times the normal value and several times the equivalence of the bicarbonate of extra cellular fluids This relationship is important first because alkalosis will

RELATION OF SERUM BICARBONATE TO INTRACELLULAR SODIUM AND POTASSIUM IN ONE KILOGRAM OF TISSUE

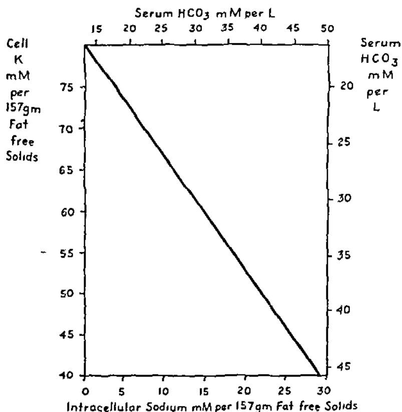


CHART III Relation of the concentration of serum bicarbonate to intracellular sodium and potassium of muscle The line shows the relation of intracellular sodium to potassium the bicarbonate concentrations on the ordinate are the best fit for intracellular potassium while those on the abscissae are the best fit for the intracellular sodium The values for intracellular sodium and potassium are for the same amount of intracellular fluid used for 1 kilogram of tissue in Charts I II and IV

tend to persist if potassium cannot be replaced and second because deficit of potassium will result in alkalosis even in the presence of abundant sodium chloride. Examples of both of these events will be cited later. On the other hand acidosis produced by loss of sodium alone leads to deficits of this ion not only in the extracellular fluids but also in the cells. It is this combined deficit that measures the amount of sodium bicarbonate that must be retained in order to restore the concentration of bicarbonate in serum. Thus acidosis resulting from loss of sodium without loss of potassium will have an extracellular deficit equal to the decrease in bicarbonate concentration multiplied by the volume of extracellular water, i.e. $(25 - 5) \times 0.25 = 5$ mM of sodium per kilogram of body weight if the serum bicarbonate is 5 mM per liter. In addition there would be a deficit of about 7 mM of sodium in the cells making a total deficit of about 12 mM per kilogram of body weight.

Clinically, chloride is relatively deficient if the concentration in serum is low, but the loss may occur alone or in conjunction with deficit of potassium or as a result of deficit of potassium. Low concentration of bicarbonate indicates a loss of sodium from extracellular fluids unless there is an accumulation of other ions displacing bicarbonate. However, the decrease in bicarbonate does not reveal the state of intracellular sodium, since if there is deficit of potassium there may be high intracellular sodium in the presence of acidosis. *Deficit of* potassium can be proved only by demonstrating a greater relative loss of potassium than nitrogen during the development of the condition or a greater relative retention of potassium than nitrogen during recovery. If body water and circulation are relatively normal, deficiency of potassium is likely to be accompanied by low concentration of potassium in serum.

The physiochemical factors controlling the acid base equilibrium of the blood have been discussed adequately in a recent paper by Singer and Hastings[9] and in textbooks.[10] The present discussion will therefore emphasize the relationship of the changes in acid base equilibrium of the blood to alterations in the composition of extracellular fluids and the accompanying changes in the cells.

Changes in the acid base equilibrium may be defined as deviations from normal in the reaction or pH of the blood. The pH is determined by the ratio of the carbon dioxide to the bicarbonate of plasma. The concentration of carbon dioxide depends on the partial carbon dioxide pressure of arterial blood which is normally equilibrated with the

carbon dioxide of residual alveolar air. Hence the carbon dioxide tension is subject to the regulation of pulmonary ventilation by the respiratory center. The concentration of bicarbonate in plasma is dependent on the amount of cations available to form bicarbonate at the particular carbon dioxide tension with the particular amounts of blood electrolytes and organic buffers. The cations available to form bicarbonate are regulated by the kidneys. Inasmuch as we are chiefly concerned with the content of water and electrolyte in body fluids, we shall neglect the relatively small changes in the buffering effects of the plasma proteins, red cells and phosphate and emphasize the contents of the tissues in sodium, potassium and chloride. These ions are the chief factor determining the major clinical disturbances in the amount of cations available to form bicarbonate. The cations available to form bicarbonate are the algebraic sum of the total cations minus the plasma anions excluding bicarbonate, i.e., $(Na + K + Ca + Mg) - (Cl + HPO_4 + \text{proteins} + \text{sulphate} + \text{lactate} + \text{keto acids} - - - -)$. For many purposes the changes in cations available to form bicarbonate in the body as a whole are adequately defined by the balances of sodium plus potassium minus chloride.

Metabolic Acidosis

Metabolic acidosis is primary decrease in the cations available to form bicarbonate. It may be produced by relative increase in the concentration of anions or relative decrease in the concentration of cations. An increase in anions may arise as a result of ingestion of acidifying salts or through the endogenous production of organic acids owing to exercise, anoxia, hemorrhage, keto acids in starvation ketosis and diabetic acidosis or the retention of phosphates and sulphate in renal insufficiency. A relative deficit of cations may result from losses of intestinal secretions, biliary secretions or through abnormal renal excretion.

The changes in intracellular electrolytes in metabolic acidosis are only beginning to be studied. Deficit of sodium alone, such as is illustrated in chart III, apparently is relatively rare. It has been shown that feeding protein milk to premature infants leads to retention of chloride and little change in body sodium[11, 12]. The change in the acid base equilibrium and the balances demonstrates that practically all the intra-

cellular sodium is transferred to the extracellular fluids under these circumstances The resulting change in intracellular composition must be about the same as is illustrated for deficit of sodium in chart III Acidifying salts such as ammonium chloride and calcium chloride probably produce similar changes In one baby subjected to protein milk feeding for six days the balances showed losses of intracellular potassium during the last three days It is likely that acidosis resulting from loss of sodium first leads to deficits of sodium in the extracellular and intracellular fluids and later losses of potassium may develop Under these circumstances sodium may be transferred back into the cells and aggravate the acidosis Thus acidosis beginning as primary sodium deficit tends ultimately to produce depletion of potassium and water

Metabolic acidosis usually is accompanied by deficits of water sodium potassium and chloride When there is acidosis and deficit of potassium intracellular sodium apparently remains normal or may even be somewhat high but not as high as when there is a similar deficit of potassium and no acidosis The difference between the deficits of sodium and potassium and the deficit of chloride is a measure of the relative deficiency of cations available to form bicarbonate Since the deficit of potassium may be greater than total normal extracellular bicarbonate plus normal intracellular sodium most cases of acidosis cannot be treated rationally with sodium chloride and sodium bicarbonate alone If intracellular potassium remains low the amount of sodium in excess of chloride required to restore extracellular bicarbonate would be more than the normal excess of sodium over chloride including intracellular sodium The changes in tissue composition in metabolic acidosis indicate clearly that replacement of potassium as well as sodium and chloride is necessary in most cases

Metabolic Alkalosis

Metabolic alkalosis is produced by primary increase in sodium available to form bicarbonate in plasma Although metabolic alkalosis may be produced by relative excess of sodium it usually results from relative deficit of chloride The commonest cause is loss of gastric juice by vomiting or suction drainage after operations If sufficient water is available to permit renal adjustment potassium will tend to be lost from the cells and sodium will partially replace the intracellular deficit of

potassium If the plan of therapy offers no opportunity for the body to replace the deficiency of potassium alkalosis may continue despite the administration of sodium chloride because the biological adjustment to deficit of potassium leads to maintenance of alkalosis by the kidneys A similar reaction by the kidneys explains the development of alkalosis as a result of primary deficiency of potassium In either case recovery from alkalosis requires the replacement of potassium as well as chloride

Respiratory Acidosis

Respiratory acidosis results from primary increase in serum carbon dioxide tension Probably the most frequent cause is depression of pulmonary ventilation owing to narcosis injury to the respiratory center or paralysis of the muscles of respiration However both acute and chronic respiratory acidosis may be produced by diseases of the lungs leading to thickening of the alveolar walls exudates bronchiectasis and emphysema Since oxygen diffuses less rapidly than carbon dioxide the arterial blood becomes less saturated with oxygen than normal when carbon dioxide accumulates Presumably there is no change in body electrolyte in uncompensated respiratory acidosis

Respiratory Alkalosis

Respiratory alkalosis results from primary decrease in carbon dioxide tension It is produced by excessive pulmonary ventilation such as occurs during exercise fever and disturbances in the respiratory center as a result of infections of the central nervous system tumors and drugs (salicylates) Overventilation may occur in hysterical patients or as a result of anoxia in cardiac failure and at high altitudes Uncompensated respiratory alkalosis presumably results in no change in body electrolytes

The *disturbances in acid base equilibrium* have been discussed above as if only the carbon dioxide tension or the cations available to form bicarbonate were altered Actually the alteration of one of these variables leads to compensatory variations in the others In metabolic acidosis the respiratory center responds to the low pH by increased pulmonary ventilation which reduces the carbon dioxide tension The reduction is not sufficient to produce a normal pH in the blood In

metabolic alkalosis the respiratory center may reduce pulmonary ventilation but the reaction is limited because anoxia tends to be produced and again stimulates increased respirations

On the other hand the kidneys may alter the cations available to form bicarbonate in both respiratory acidosis and alkalosis In respiratory alkalosis the serum bicarbonate may be reduced fairly rapidly but as long as the disturbance in pulmonary ventilation persists, the blood pH remains normal or slightly alkaline However after the kidneys have reduced the available cations the respiratory center may recover and respond normally The patient then will suffer from true metabolic acidosis Since recovery from the effects of drugs such as salicylates may be rather rapid respiratory alkalosis is likely to go through a phase of metabolic acidosis during recovery

In respiratory acidosis the kidneys may increase the cations available to form bicarbonate to quite high figures (45 mM per liter) The blood pH remains more acid than normal and arterial blood shows diminished oxygen saturation In respiratory acidosis due to lung disease recovery of lung function is unlikely to be sufficiently rapid to produce true metabolic alkalosis

It is not known whether compensated respiratory alkalosis and acidosis lead to changes in cell sodium and potassium It is likely that such is the case and that compensated respiratory acidosis produces increase in cell sodium and decrease in cell potassium Compensated respiratory alkalosis is likely to lead to loss of intracellular as well as extracellular sodium

Disturbances in body water and electrolyte involve changes in the volume and electrolyte concentration which are just as important as the changes in acid base equilibrium Dehydration usually involves decrease in body electrolyte and loss of electrolyte tends to cause losses of water If the losses of electrolyte are proportionately greater than the losses of water there is a decrease in the concentration of electrolyte in serum This type of disturbance may be called hypotonic dehydration

Hypotonic Dehydration

Methods are available for study hypotonic dehydration due to loss of electrolyte with little change in body water[11] Loss of extracellular electrolyte without significant change in body water produces decrease in the concentration of sodium and chloride in serum while

the concentration of proteins in serum and red cells in blood are increased The plasma volume is markedly reduced The animals look sick refuse to eat and are weak The volume of urine decreases the rate of glomerular filtration is reduced to quite low figures the non protein nitrogen rises Water and sodium are excreted more slowly than normal[1] The cardiac output is strikingly reduced[14] It can be shown that the volume of extracellular water decreases while the volume of intracellular water increases The changes in distribution of water are dependent on the adjustment of the osmotic pressure in the intracellular fluids by shifts of water rather than by losses of electrolyte from the cells The animals are in a shock like state and do not withstand bleeding as well as normal animals[1] The clinical picture is essentially the same as that of the usual dehydration seen in patients The experiments are important because they emphasize that the central feature of hypotonic dehydration is loss of extracellular electrolyte

For practical purposes hypotonic dehydration may be considered to result from the loss of proportionately more electrolyte than water although rare cases may involve little or no deficit of water With low concentrations of electrolyte in serum the cells of the body contain more water than is normal Statistically the increase in intracellular water in experiments involving losses of extracellular electrolytes is only about two thirds as much as would reduce the electrolyte concentration of the intracellular fluids of muscle as much as the reduction of extracellular concentration[18] In chronic states in patients the relationship has not been studied but may be somewhat different In any case the disturbances in circulation renal function and muscular strength are dependent not only on the reduction in extracellular water and plasma volume but also on the decrease in electrolyte concentration[16] Hypotonic dehydration produces the picture of medical shock and responds to replacement of electrolyte but the response is somewhat better when blood or plasma as well as electrolyte is given[19]

Hypertonic Dehydration

Hypertonic dehydration results when the loss of water is proportionately greater than the loss of electrolyte This leads to increase in the concentration of electrolyte in serum It can be shown that relatively pure increase in extracellular electrolyte produces increase in

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tions and acid base equilibrium of the plasma are altered as has been shown to be the case, when there is no increase in extracellular volume Thus hypotonic edema should produce increased hydration of the cells while hypertonic edema should lead to dehydration of the cells There is also evidence that low electrolyte concentration in patients with edema leads to circulatory failure similar to that seen in hypotonic dehydration Renal function and circulation may be improved by raising the electrolyte concentration by giving sodium chloride and sodium bicarbonate It is likely that some of the cases of edema show the changes in intracellular composition illustrated in chart III when there is a disturbance in bicarbonate concentrations produced by a primary relative deficiency of one ion

Changes in Tissue Composition

With the above background based largely on studies of experimental animals the changes in tissue composition in certain conditions in patients will be discussed briefly It must be realized that actual values for patients are difficult to obtain and that the methods are subject to errors not involved in tissue analyses The composition of tissue of patients can be inferred by measuring the losses during development of the disturbance or by measuring the retentions during recovery Since it has seldom been possible to determine the skin losses the balances usually are incomplete However this lack of complete balance does not preclude approximate estimations of the changes in body composition

The experiments on animals indicate that the magnitude of the losses of extracellular electrolyte in patients probably never is greater than one third of the normal content i e about 9 mEq of Cl and 1 mEq of Na per kilogram of body weight in babies or 6 and 10 in adults This conclusion is based on the fact that losses that are this great in cats and dogs lead to symptoms that simulate those seen in the sickest patients Loss of half of the extracellular electrolyte apparently was more than the animals could withstand[14] The experiments on potassium deficiency in animals indicate that only as much as half of the potassium of muscle may be replaced by sodium Neglecting deficits in other tissue this would indicate that the maximum deficit of potassium could

extracellular water and dehydration of the cells[11] Patients with hypertonic dehydration may show symptoms of shock, but circulatory failure is much less prominent than in hypotonic dehydration The patients are likely to show hyperpnea mental symptoms and fever[9] Patients and experimental animals with hypertonic fluids show evidence of cerebral damage, death is likely to be preceded by high fever and arrest of respiration

As will be pointed out later, symptoms develop when serum potassium rises to about twice the normal concentration When the level of serum potassium increases the concentration of potassium in cells rises[5] However if animals are given diets high in potassium the compositions of the cells remain essentially normal If rats are given water containing potassium chloride at greater concentrations than can be excreted by the kidneys they refuse to drink If potassium chloride is injected into the peritoneal cavity the concentration in the serum rises in proportion to the amount injected Accompanying this rise there is an increase in the intracellular potassium If the potassium does not produce fatal intoxication in 60 to 90 minutes the rats survive If they live for about 18 hours compensatory excretion leads to low normal potassium in the muscle From these facts it can be seen that high intracellular potassium probably does not occur except when extracellular potassium is also high

Edema

The term edema should be limited to expansion of extracellular water and electrolytes As will be pointed out later edema may develop from disturbances in the exchange between the capillaries and interstitial fluids However, the large expansions of extracellular fluids are accompanied by evidences of failure of the kidneys to excrete sodium The expansion of water in extracellular fluids may be so great that half of the body weight is extracellular The edema may be accompanied by acidosis, alkalosis or low electrolyte concentrations Although increase in electrolyte concentration usually leads to further expansion of body fluids so as to reduce the electrolyte concentrations hypertonic concentration may be found in edematous patients While the actual composition of the intracellular fluids in the presence of edema has not been studied it is usually assumed that the intracellular structures are well preserved However there is no reason to doubt that the cells undergo the same sort of changes in composition when the concentra

95 mM of sodium and 10 mM of potassium The effect of such deficits on the body composition of a normal infant is shown in chart IV Since the deficiency of sodium for the body as a whole is equivalent to the deficiency of chloride the acidosis is explained by transfer of extracellular sodium to the cells This conclusion is evident from the fact that the low concentration of bicarbonate indicates relative deficiency of sodium in extracellular fluids

The deficiency of potassium is equivalent to about one seventh of the total estimated intracellular potassium content of normal babies or to about the equivalent of one fourth of the normal extracellular sodium Although intracellular sodium is abnormally high the intracellular sodium is not as great as the deficit of potassium would predict in chart III The deficiency of potassium is sufficient to explain the acidosis developing with no relative deficit of sodium in relation to chloride The acidosis in infantile diarrhea is therefore dependent on deficit of potassium occurring in patients with deficiency of water sodium and chloride

The studies do not show the actual changes in tissue composition in infantile diarrhea since the state of nutrition of the patients usually is greatly disturbed The older literature showed that babies dying of diarrhea have a great loss of intracellular structures which apparently leave extracellular fluids relatively large in relation to body weight[1] However the authors have analyses of muscles that confirm the changes in intracellular composition indicated by the balance studies Since the diagram is based on the estimated losses subtracted from a hypothetical normal composition it does not indicate the changes in tissue composition that are produced by undernutrition The diagram should therefore be considered to represent the composition only in a well nourished baby with acute diarrhea The deficit of extracellular water and electrolyte is about one fourth of the normal content Intracellular sodium is about double the normal value The deficit of water in the cells is a little greater than that of extracellular fluids

Inspection of the diagram enables one to visualize the results of various types of treatment If the infants are treated with sodium chloride and water alone the deficit of potassium will persist and sodium will enter the cells owing to persistence of the deficiency of potassium If sufficient water is available to permit renal adjustment high intracellular sodium and low intracellular potassium leads to alkalosis High concentration of bicarbonate in serum also aggravates the tendency to

be about 14 mM per kilogram of body weight. It is unlikely that values greater than 17 will be found in patients.

Infantile diarrhea produces deficits of water, sodium, potassium and chloride which show considerable variations in the absolute and relative

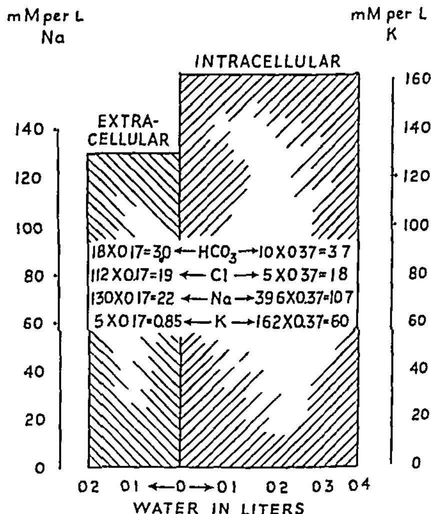


CHART IV. Diagram of 1 kilogram of tissue in infantile diarrhea. The deficits are 125 gm of water, 9 mM of chloride, 9 mM of sodium and 10 mM of potassium.

losses of these constituents. The plasma may be hypotonic or hypertonic. Metabolic acidosis usually is present in the severe cases. The balances during recovery in 8 severe cases showed average retentions per kilogram of body weight of 125 grams of water, 9.2 mM of chloride

which was accompanied by low concentrations of potassium in serum and was relieved by potassium salts The authors found that the retentions during *recovery in a severe case of diabetic acidosis in an 8 year* old girl were 100 grams of water 8 mM of chloride 12 mM of sodium and 6 mM of potassium per kilogram of body weight The serum concentrations of phosphorus decrease somewhat more strikingly during recovery from diabetic acidosis than those of infants with diarrhea The changes in tissue composition in diabetic acidosis apparently resemble those of infantile diarrhea except for the hyperglycemia and ketosis Recent observations[31] *indicate that the elevation of blood sugar* expands extracellular fluids and dehydrates the cells owing to its osmotic effect Since the glucose is only found in the extracellular fluids it can exert its osmotic effect only in these fluids A blood sugar of 550 mgm per 100 ml has about one tenth as great osmotic pressure as that of normal plasma These facts must be taken into account in judging the decrease in serum electrolyte concentrations in diabetic acidosis

The acidosis of *renal failure* has not been studied adequately from the point of view of changes in both extracellular and intracellular composition Nephritic patients frequently show low serum concentrations of bicarbonate chloride and sodium but the intracellular changes accompanying these changes are not known The usual explanation of the serum electrolyte changes is failure of the kidneys to conserve sodium chloride and preserve the acid base balance in advanced hyposthenuric nephritis Certain patients with chronic nephritis have shown weakness which is relieved by potassium salts These patients have low concentrations of potassium in serum[32] and analyses of other nephritic patients with acidosis have shown low potassium in muscles[31] *The logical explanation is that the kidneys are unable to* conserve potassium These findings suggest that deficit of potassium may aggravate acidosis through transfer of extracellular sodium to the cells in patients who already have low concentrations of sodium and chloride in serum Thus the acidosis of nephritis may depend on deficits of both sodium and potassium without deficiency in water However when there is oliguria the concentration of potassium in serum may rise to levels associated with disturbances in the heart[31, 33, 36] Indeed potassium intoxication is one of the events leading to death in experimental anuria[3] and in some cases of nephritis[38] The intracellular fluids of such patients probably are high in potassium

All the disturbances produced *by loss of extracellular water and*

development of low serum calcium. All these disturbances will disappear when food with its high content of potassium can be absorbed. Indeed the success of treatment with solutions containing sodium chloride and sodium bicarbonate depends on sufficiently rapid recovery to permit feeding.

If sodium chloride is given with insufficient water to permit renal adjustment, acidosis may persist or be aggravated. Case 3 of a previous study illustrates this course of events.[1] The patient was admitted for severe diarrhea which had been treated at home by the addition of small amounts of sodium chloride to a milk mixture that gave too little water for a baby with diarrhea. On admission the concentrations of bicarbonate and chloride in serum were respectively 7 and 123 mM per liter. During recovery no sodium and chloride were retained while 13 mM of potassium and 100 gm. of water per kilogram of body weight were added to the body. Since the diarrhea would have led to losses of sodium and chloride at home if sodium chloride had not been added to the food, this treatment had prevented deficits of these ions. The acidosis probably had been aggravated by transfer of sodium to the cells since sufficient water was not available to permit renal adjustment. The persistent deficit of potassium explains the transfer of sodium to the cells. On entry into the hospital the patient suffered chiefly from deficit of water and potassium leading to acidosis and hypertonic dehydration. The picture was the result of treating diarrhea with sodium chloride and insufficient water. A similar picture is seen frequently when acidosis is treated with saline and insufficient water free of electrolytes.

Adults with diarrhea have not been studied by methods which demonstrate the actual deficits of water and electrolyte. Nevertheless it has long been known that adults lose large amounts of water, sodium, potassium and chloride in dysentery and cholera.[4] The importance of losses of potassium is indicated by the observation of paralysis following the treatment of cholera.[5] This paralysis was relieved by the intravenous injection of potassium chloride. Similar observations have been made in sprue.[6] There can be little doubt that diarrhea in adults leads to striking deficits of potassium as well as of sodium and chloride and water and that the changes in tissue composition are similar to those of infants.

About twenty years ago Atchley and others showed that *diabetic acidosis* is associated with losses of potassium as well as sodium and chloride. Holler and others[8, 9, 10] observed paralysis during recovery

the presence of high intracellular sodium in alkalosis indicates that the relative excess of sodium over chloride in the body as a whole is much greater than that which is revealed by analysis of the serum for chloride and sodium The large amount of intracellular sodium explains the slow response of some cases to administration of sodium chloride The fact that potassium deficit persists means that in accordance with the relationships depicted in chart III the kidneys will not excrete sodium so as to increase the bicarbonate in the serum until cellular potassium is replaced

Prolonged *gastric suction* after operations provides the conditions for the development of alkalosis with potassium deficiency The removal of gastric fluid depletes the body of more chloride than sodium and produces alkalosis The administration of sodium chloride facilitates the excretion of potassium by the kidneys While sodium chloride usually is administered in sufficient amounts to replace extracellular electrolyte the development of potassium deficiency alters the renal function so that metabolic alkalosis persists Patients subjected to gastric suction are likely to develop low concentrations of potassium in serum Clinical improvement follows replacement of potassium as well as sodium chloride[illegible]

McQuarrie and others[illegible] first called attention to certain cases of *Cushing's syndrome* which have alkalosis refractory to administration of sodium chloride and ammonium chloride but responding to potassium salts The serums show not only high concentrations of bicarbonate but low chloride and potassium Kepler and others[illegible] studied one patient who recovered from alkalosis after removal of an adrenocortical tumor but again developed alkalosis when metastases became manifest Analyses of the muscle of these cases probably would show low potassium and high intracellular sodium The patients suffer from primary deficit of potassium produced by certain adrenocortical steroids which increase the excretion of potassium by the kidneys The same picture can be produced by repeated injections of desoxycorticosterone acetate and less readily by diets low in potassium The experimental animals receiving desoxycorticosterone show high intracellular sodium and low muscle potassium together with marked alkalosis of the serum The administration of cortisone and adrenocorticotropic hormone involves loss of potassium and alkalosis Part of the effect of operations in producing losses of potassium may be increased stimulation of the adrenal cortex[illegible]

electrolyte may result from the immobilization of water and electrolytes at the site of an *exudate* or *tissue injury*. Burns and crushing injuries to muscles are examples of disturbances of this type which involve no loss of water from the body.[39] It has been shown that the fluids that accumulate at the site of injury contain all the essential elements of extracellular fluids and plasma. Although the fluids are not lost from the body as a whole, the water and electrolytes are not available to the rest of the tissues. Thus it is not surprising that traumatic shock with immobilization of extracellular water and electrolytes shows the same clinical phenomena of peripheral circulatory collapse, oliguria and anoxia of the tissues as are encountered in medical shock produced by losses of extracellular electrolytes and water.

When the circulation is interrupted or impaired by *shock* or *exposure to cold*,[10, 11] the intracellular fluids of the muscles lose potassium and gain sodium. As was pointed out earlier, transfer of extracellular sodium to the cells produces metabolic acidosis when there is failure of renal adjustment of body electrolyte. The cellular loss of potassium raises the concentration of potassium in serum. If renal function is adequate, the potassium will be excreted in the urine.

A similar exchange of potassium for sodium in the cells takes place in *anoxia* and explains the rise in the concentration of potassium in serum in peripheral vascular collapse. High concentrations of potassium in serum are found frequently in diarrheal dehydration and diabetic acidosis before treatment is initiated despite the fact that the intracellular fluids are deficient in this ion. This sort of reaction, leading to urinary excretion of potassium, explains in part the loss of this ion in these and other similar conditions. However, the chief interest lies in the fact that internal shifts of sodium as well as loss of sodium from the body act together to produce acidosis.

Alkalosis usually is produced by primary deficit of chloride resulting from *vomiting*. The authors have determined the retentions during recovery in 4 cases of congenital hypertrophic stenosis. In all there was evidence of abnormally high intracellular sodium before treatment. Three patients retained moderate amounts of potassium during recovery, while one did not. Danowski and others[4] have shown by balances that more potassium is retained during recovery than can be accounted for by the retention of nitrogen. Apparently some cases of alkalosis due to deficit of chloride get enough potassium from food to prevent deficits of this ion, but others develop large deficits of potassium as well as large losses of chloride in relation to sodium.[43] It should be remembered that

the presence of high intracellular sodium in alkalosis indicates that the relative excess of sodium over chloride in the body as a whole is much greater than that which is revealed by analysis of the serum for chloride and sodium The large amount of intracellular sodium explains the slow response of some cases to administration of sodium chloride The fact that potassium deficit persists means that in accordance with the relationships depicted in chart III the kidneys will not excrete sodium so as to increase the bicarbonate in the serum until cellular potassium is replaced

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Edema represents chiefly expansion of the extracellular water and electrolyte. The mechanism promoting the formation of edema, which acts locally in the exchange of the fluid between the capillaries and the interstitial fluids are as follows: increased hydrostatic pressure in the capillaries in heart failure and venous obstruction; decrease in serum protein concentration in nutritional edema, nephrosis, nephritis and liver diseases, the presence of abnormal amounts of proteins in interstitial fluids in allergic reactions, myxedema and acute nephritis and decreased absorption of fluids by the lymphatics in some diseases. Ultimately the volume and concentration of body fluids are controlled by the kidneys. Disturbances in the excretions of sodium play an important role in the genesis of edema which is discussed in a subsequent part of this chapter.

The Expenditure of Water and Electrolyte

The intake of water and electrolyte must equal the losses. For this reason knowledge of the physiological factors controlling expenditure enables the physician to plan rationally an intake that meets these demands. The important pathways of expenditure of water and electrolyte are (1) the lungs and skin, (2) the gastrointestinal tract and (3) the urine.

Losses from Lungs and Skin

The losses from the lungs and skin may be divided into the insensible losses occurring when there is no sweat and those involving activity of the sweat glands. The insensible water loss excluding sweat is roughly correlated with heat production so that 4[illegible] grams are lost for each 100 calories produced.[1] When there is no sweat, a small amount of electrolyte is also lost from the skin, but this is negligible for most purposes.

Stool Water

Stool water is dependent chiefly on the residue of the diet which, in general, is proportional to the caloric intake. During fasting stool water is negligible unless there is diarrhea. Normal fecal water is about 4 grams per 100 calories of the diet and is such a small part of the total water expenditure as to be negligible for most purposes.

[1] Vol I 152

Kidney Excretion

The volume of urine must be sufficient to remove the excretory load presented to the kidneys. The substances presented for excretion are chiefly the end products of protein metabolism together with other osmotically active substances of which electrolytes are the most important. Renal load is proportional to the metabolic mixture being burned or the intake. Although different diets contain variable amounts of protein and electrolytes, the ordinary diets of patients are sufficiently alike to permit an approximate estimation of the renal load from caloric intake. During fasting the renal load consists largely of the end products of protein metabolism together with electrolyte freed by the breakdown of tissues. The metabolic mixture during fasting probably varies somewhat with age, the nutritional state and the length of fast. When all other food is omitted, administration of glucose reduces the renal load not only to the extent that protein is spared but also by abolishing ketosis which requires excretion of these acids together with electrolyte.[3] Minimal protein metabolism is attained by giving 4 to 5 grams of carbohydrate per 100 calories metabolized. In other words the renal load during fasting is proportional to the caloric expenditure except that the load is diminished to a minimum by the administration of glucose. The concentration of the urine determines the volume of water required to contain a given load. The volume of urine is therefore dependent on the ability of the kidneys to form urine of varying specific gravity, on the renal load and the intake of water. Knowledge of these relationships enables the physician to estimate the volume of urine which will contain the substances presented to the kidneys for excretion and to plan an intake that will meet the expenditure.

Chart V shows the urinary volume per 100 calories on the ordinate and the urinary concentration on the abscissa. The area labeled diet gives the urinary volumes for the usual adult diet. The area marked glucose gives the urinary volumes during omission of all food except enough glucose to produce maximal reduction of renal load. Complete fasting requires intermediate volumes. Artificially fed infants fall into the lower part of the area marked diet. Owing to the low content of protein and electrolyte in human milk, the renal load of breast fed infants is almost as low as that indicated by the glucose area.

Chart V may be used to calculate the water requirement as follows: (1) the area appropriate for the diet, fasting or glucose administration is chosen. ( ) from the chart the urinary volume per 100 calories is

obtained for an appropriate concentration usually at a specific gravity of 1 012, (3) the caloric production is estimated from the age weight activity and food intake, (4) the volume of urine per 100 calories multiplied by one hundredth of the estimated caloric production gives the total urinary volume (5) for each 100 calories metabolized 42

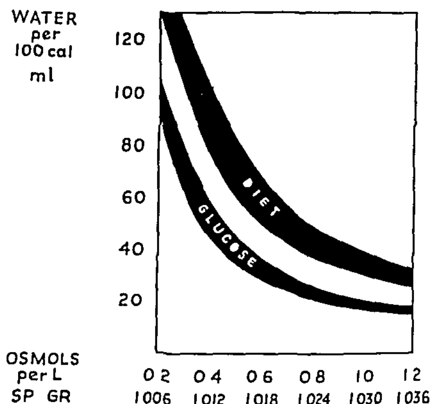


Chart V *Urinary water per 100 calories of food or 100 calories of heat production* as related to urinary concentration The area marked diet gives the renal load per 100 calories of the usual adult diet while the area marked glucose gives the renal load per 100 calories of heat production when maximal protein sparing is produced by glucose administration during omission of all other food

grams of water is required to cover the insensible water losses The sum of the total urinary volume and the insensible water losses gives the water expenditure excluding sweat stool water and abnormal losses Since complete absence of perspiration is unlikely 15 to 20 ml per 100 calories metabolized should be added to cover total water expenditure in the absence of abnormal losses or large volumes of sweat

For the normal individual without sweat on a normal diet and having a urinary specific gravity of 1.01, the above calculations indicate that water expenditure is 126 grams per 100 calories or 140 grams assigning a small allowance for sweat and stool water. Since babies metabolize about 100 calories per kilogram of body weight, this figure gives the water requirement of infants per kilogram of body weight. An adult metabolizing 3,000 calories would require 3,800 to 4,200 grams or about 54 to 60 grams per kilogram of body weight if the caloric expenditure is 43 calories per kilogram. If the values are calculated for a urinary specific gravity of 1.024, a baby would require 88 grams per kilogram of body weight if there is no sweating. An adult would require 2,650 grams or 38 grams per kilogram of body weight. These figures are about minimal except as modified by reduced caloric production or diets giving low renal loads. It should be noticed that calculation of the water expenditure at a specific gravity of 1.01 provides sufficient water for considerable sweat if the kidneys are able to form a concentrated urine. In the calculation of the water intake it should be kept in mind that the water available for expenditure is equal to the preformed water intake plus the water of oxidation. The latter is about 12 grams per 100 calories metabolized of the usual metabolic mixture. During fasting a small amount of water is made available for expenditure by decrease in tissue water.

The usually prescribed intake of infants is 150 grams per kilogram which would lead to a urinary specific gravity of 1.008 if there is no sweat or abnormal losses. A similar intake per 100 calories metabolized in an adult would be 4,500 grams. At this level of intake the kidneys could, if so required, provide 62 grams of water per 100 calories metabolized for sweat or abnormal losses or a total of 1,860 for the average adult. This level of intake apparently is appropriate for most infants since they cannot readily make known their need for water. It may be advisable to prescribe as high an intake as this for children and adults if sweating or abnormal losses are likely to occur. Adults will voluntarily regulate their intake so as to lead to moderately concentrated urine.

Unless there is considerable sweating or abnormal losses, the intake of electrolyte with the diet or freed from breakdown of tissues during fasting is sufficient to replace the losses through the skin, stools and urine. The urine can be rendered practically free of sodium and chloride. Data on the ability of the kidneys to conserve potassium are meager, but it appears that the normal kidney can form a urine which

contains potassium at no greater concentration than that of serum. With maximal conservation of electrolyte by the kidneys the urinary losses are about 0.2 mM of chloride and sodium and 0.4 mM of potassium per 100 calories metabolized. The minimal daily losses in a year old infant are about 2 mM of sodium chloride and 4 mM of potassium. Corresponding losses for an adult would be four- to sixfold.

When food is taken the stool losses are about 0.1 mM of sodium chloride and 0.4 mM of potassium per 100 calories metabolized. Stool electrolyte is negligible during fasting unless there is diarrhea.

Metabolic studies indicate that the insensible water losses are slightly greater than can be accounted for by the calorie production under ordinary circumstances in infants[31] children[5] and adults[1]. This finding indicates that a moderate amount of sweat usually is being formed. An average estimate is 10 grams of water 0.5 mM of sodium and chloride and 0.2 mM of potassium per 100 calories metabolized. The average sweat losses in adults would be 300 grams of water, 15 mM of sodium chloride and 6 mM of potassium per day.

Allowance of water and electrolyte for growth is of little practical significance inasmuch as the usual diet provides abundant water and electrolyte. The daily retentions during the first year of life are 10 grams of water 0.6 mM of sodium 0.4 mM of chloride and 1.6 mM of potassium. During periods of rapid growth the retentions may be twice these values and from the third to tenth year about half as great.

Summary

In summary the water requirements can be predicted fairly confidently for normal conditions by the calculations described in the discussion of chart V. The minimal losses of electrolyte are about 1.3 mM of sodium potassium and chloride per 100 calories metabolized. This indicates that the minimal requirements in the first year are about 0.5 grams of sodium chloride and 0.31 grams of potassium (0.6 grams of potassium chloride). An average adult would require 1.5 grams sodium chloride and 2.9 grams potassium chloride. Usually somewhat larger amounts should be given since minimal expenditure cannot be anticipated. When all fluids are given parenterally, there is evidence that losses of potassium exceed the minimal losses by a considerable amount. This has been found to be the case when patients are given all fluids parenterally after operations. The amount required seems to be to

2 5 mM per 100 calories metabolized i e about 50 mM K (3 7 grams potassium chloride) per day in the average adult

Abnormal Losses of Water and Electrolyte

Under normal conditions without sweating about two thirds of the insensible water loss occurs by diffusion through the skin The rate of water loss from the respiratory tract depends on the volume of respiratory exchange and the contents of water in the inhaled and exhaled air These are in turn dependent on the temperature and humidity of the environmental air since the exhaled air is about 88 per cent saturated at body temperature When there is hyperpnea the magnitude of the water losses through the lungs is difficult to measure but probably reaches values five times as great as the normal rate[6] In estimating the importance of the losses of water from the lungs it should be remembered that an increase in the loss by the lungs may be partially compensated by decrease in the activity of the sweat glands Water loss from the lungs is not accompanied by loss of electrolyte

The insensible loss of water through the skin is dependent chiefly on the gradient for diffusion through the skin This is dependent on the skin temperature if the skin is dry A small amount of electrolyte is lost from the skin when there is no sweat presumably through desquamation though there may always be a minimal activity of the sweat glands

Sweat

The factors leading to the production of sweat are discussed in the excellent book by Adolph and associates In the thermal balance of the body the skin acts like a black body with a temperature of 33 3 degrees centigrade (92 F) The body gains heat from the environment and objects above this temperature and loses heat to objects and environment below this temperature Under conditions leading to minimal water losses from the skin about one fourth of the heat loss from the body is accounted for by the insensible losses of water At an environmental temperature of about 26 7 degrees centigrade (80 F) body temperature is maintained without sweating and without greater production of heat than that characteristic of rest At a given temperature the radiant energy of direct sunshine may add as much as 50 per

cent to the heat balance when only the indirect energy from the sky is acting on the body. Sweat is produced normally in amounts sufficient to maintain body temperature when the metabolic production of heat and the positive heat balance from the environment are greater than the losses produced by evaporation of the insensible water and the heat losses through radiation, conduction and convection. At low temperatures the insensible losses cannot be decreased so the heat balance is maintained by increased heat production or prevention of loss by clothing. The efficiency of the evaporation of sweat is not seriously impaired until humidity is greater than 80 per cent. Air currents accelerate the rate of evaporation and the exchange of heat with the environment.

The volume of sweat may reach 2.4 liters an hour in man at hard work at a high environmental temperature. A few measurements on normal infants kept practically nude showed that raising the environmental temperature from 26.7 to 33.3 centigrade (80 to 90 F) increased the loss of water from the lungs and skin from 48 to 108 grams per kilogram of body weight per day.[1] Presumably at least as much as 60 grams of sweat per kilogram per day was produced at the higher temperature. Adults sitting in the shade at similar temperatures showed comparable sweating per unit of heat production. The calculated losses of sweat in infants with diarrhea studied at comparable temperatures in August in Galveston and Dallas averaged 70 grams per kilogram of body weight per day.[3]

When the environmental temperature is higher than 33.3 degrees centigrade (92 F.) all the loss of heat is accounted for by the evaporation of water. Light clothing diminishes the amount of sweat at high temperatures by prevention of loss of drops of sweat from the body surface and decrease of the addition of heat from the environment. At lower temperatures clothing sometimes increases the volume of sweat by decreasing the heat loss by radiation and convection. Mere observation of the skin is inadequate to detect the onset or to estimate the amount of sweat. For a lightly clothed individual at a room temperature of 28.8 to 32.2 (85 to 90 F.) an allowance for the loss of 50 grams of sweat for each 100 calories metabolized apparently is indicated. Since operating rooms are likely to be quite warm and the patient is kept under covers and lights giving off a good deal of radiant energy, water loss in sweat may be considerable during operations. Air conditioning of operating rooms is not a matter of comfort for the surgeons but may be a requisite for low operative mortality. Air conditioning

and avoidance of overheating are important therapeutic measures for patients suffering from disturbances in the metabolism of water and electrolyte.

The quantity of electrolyte in sweat has been found to be so variable that any prediction of the composition is difficult and unreliable. For clinical purposes the concentration of sodium and chloride may be assumed to be 5 to 50 mM per liter and that of potassium 15 mM. These values may be somewhat high for normal acclimated individuals. Actually, analyses of sweat indicate that the concentration of sodium and chloride tend to be at about equivalent concentrations and to vary *from 5 to 100 mM per liter. There is evidence that acclimatization to* hot weather is accompanied by a tendency to excrete a less concentrated sweat.[*] On the other hand, a high rate of sweating usually is accompanied by increase in the concentration of electrolyte. Recent work indicates that the concentration of sodium, potassium and chloride is influenced by adrenocortical hormones. Conn has shown that patients with adrenal insufficiency have high concentrations of sodium and chloride and low concentrations of potassium in the sweat produced in response to heat. In contrast, patients with adrenocortical tumors or ones receiving pituitary adrenocorticotropic hormone or desoxycorticosterone acetate have concentrations of sodium and chloride that are lower than normal, while those of potassium are higher than normal.

Gastrointestinal Losses

Abnormal losses of water and electrolyte from the gastrointestinal tract occur as a result of vomiting, diarrhea, escape of fluids through intestinal or biliary fistulae or by aspiration through catheters introduced into the stomach or upper intestinal tract. The approximate losses can be estimated from the volumes and the composition of the fluids lost. Chart VI shows the average concentration of certain gastrointestinal fluids. The volumes may be measured but usually can only be estimated approximately. The effect of the losses of gastrointestinal fluids is discussed ably by Gamble, particularly as they affect the composition of extracellular fluids.[*]

As the chart shows, the gastric fluid contains more chloride than sodium and appreciable amounts of potassium. As excreted by the chief cells, the chloride concentration is somewhat higher than that of sodium in serum.[61] The gastric contents are the result of mixing the acid excre-

tion of the chief cells with the neutral or slightly alkaline secretions of other cells The amount of each kind of secretion is so variable that gastric contents may contain considerably more chloride than sodium or more sodium than chloride The loss of acid gastric juice leaves the body with relative excess of sodium available to form bicarbonate in extracellular fluids This type of alkalosis is characteristic of pyloric obstruction[6]

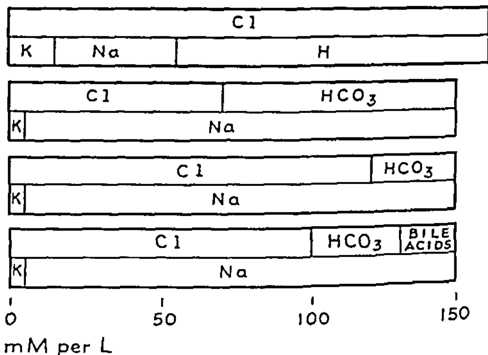


CHART VI Concentrations of gastrointestinal fluids From above downwards the following fluids are represented gastric external pancreatic small intestinal and hepatic bile

In the vomiting of renal failure and as a result of certain infections the fluid is not acid and may produce no change in acid base equilibrium or even acidosis In certain cases of vomiting typified by periodic vomiting in children, acidosis results not only because the fluid lost is not highly acid but also because starvation leads to non diabetic ketosis[63] High intestinal obstruction and loss of fluids by catheters introduced into the upper gastrointestinal tract after operations produce alkalosis

because the losses of gastric fluid are greater than the losses of intestinal juices As originally shown by Gamble there are appreciable losses of sodium in extracellular fluids even when there is alkalosis Recent work has demonstrated that considerable deficits of potassium develop As discussed in the first section of this chapter this loss of potassium results largely from changes in renal excretion The deficits of potassium following post operative suction may be so large as to produce serious symptoms[illegible] Although gastric juice contains moderate amounts of potassium it is not great enough to account for the potassium deficits

Losses of hepatic bile and the external secretion of the pancreas produce acidosis[1] Drainage from fistulae in the lower part of the small intestines may produce acidosis although intestinal juice is not highly alkaline

Diarrheal stools vary widely in composition In some patients the electrolyte concentrations are so small that little decrease in body electrolyte develops despite the loss of large volumes of water in the stools In other patients the stools contain so much water and electrolyte that the tissues are rapidly depleted of both water and electrolyte The concentrations per kilogram of stool vary from 1 to 90 mM for sodium from 10 to 110 mM for chloride and from 10 to 80 mM for potassium[3] The daily stool losses in severe infantile diarrhea are about 50 grams of water 16 mM of sodium 11 mM of chloride and 8 mM of potassium In adults cholera severe diarrhea and dysentery probably lead to comparable losses Sprue and celiac disease do not produce as severe losses of electrolyte except during periods of exacerbation Practically all types of diarrhea tend to produce greater relative losses of sodium and potassium than chloride As described in the first section the resulting metabolic acidosis depends on shift of sodium into the cells owing to deficit of potassium since sodium and chloride losses tend to be in equivalent amounts

Gamble and associates and Darrow[58] described a rare type of congenital anomaly of intestinal absorption leading to obligatory watery stools containing more chloride than sodium The patients suffered *from continual alkalosis and deficits of both chloride and potassium* Recent experimental observations indicate that rats subjected to potassium deficiency develop diarrhea in which the stools contain more chloride than sodium[8] Albright saw a similar development of alkalosis in a patient with diarrhea stools containing more chloride than sodium[58] It is likely that potassium deficit under certain circumstances alters intestinal absorption

Renal Losses

A discussion of the role of renal losses in disease is difficult, because the kidneys play the chief role in the control of the volume and concentrations of body fluids However, the renal regulation is merely the crucial activity in a complex process integrated by the regulation of the cardiovascular system The process involves the activity of the vegetative nervous system the neurohypophysis the humoral and neural control of the blood pressure and the capillary bed and both parts of the adrenal glands and other endocrine glands[69] All these influences alter renal function either directly or indirectly or both

Vascular Movements of Fluids

The movement of substances within the body and the exchange of water gases and solids with the outside environment is accomplished by the rapidly moving fluids of the vascular compartments The red cells and the blood plasma are about one fourth of the total extracellular constituents Although the red cells must be considered intracellular from the point of view of their composition their function is intimately associated with that of blood plasma Maintenance of adequate volumes of plasma and red cells is essential to normal function of the vascular system and the kidneys On the other hand disturbances in body water and electrolytes are reflected by changes in distribution of the circulation and the concentrations and volumes of plasma As noted in the first section loss of extracellular electrolyte leads to decrease in plasma volume decrease in cardiac output decrease in blood pressure and diminished renal function Increase in electrolyte concentration leads to disturbances in cellular activity particularly in the central nervous system It also increases the rate of glomerular filtration and the flow of blood to the kidneys

If the role of the kidney in controlling the volume of water and electrolyte in the body is neglected the movement of fluids between the vascular and interstitial fluids is governed by a balanced exchange[70, 71] The movement of water and diffusable ions and molecules out of the capillaries is favored by the hydrostatic pressure within the capillaries and the colloid osmotic pressure of the perivascular fluids the movement of these substances into the capillaries is favored by the colloid osmotic pressure of the plasma and the hydrostatic pressure of the perivascular

fluids which is maintained by the tissue tension An example of this balanced mechanism is seen in the portal circulation where low capillary pressure is balanced by high colloid pressure in the perivascular fluids brought about by increased permeability of the liver capillaries to protein Local alterations in the exchange of fluid may be brought about by changes in the capillary bed The lymph channels provide an alternate route for the return of vascular fluid getting into the interstitial spaces The lymph seems to be concerned particularly with the return of proteins from interstitial fluids The non renal factors controlling the distribution of body fluids explain most local accumulations of fluid While theoretically the same factors can explain generalized edema recent studies show that renal as well as non renal factors are involved in the genesis of generalized edema

Kidneys in Relation to Body Fluids

Normally the volume of fluid in the vascular compartment is adjusted to the function of maintaining the exchange of metabolites in vital organs first by redistribution of the circulation according to the need but ultimately by altering the volume of plasma and extracellular fluid [1] Present knowledge of renal physiology is inadequate to explain how the kidneys maintain the volume and concentrations of body fluid However it should be useful to point out certain mechanisms that probably are involved

According to one theory the distal tubules reabsorb sodium in quantities which are relatively constant under some circumstances If this be true the excretion of sodium could be regulated in part by changes in the rate of glomerular filtration and changes in the rate of reabsorption of water and sodium in the distal tubules Since the reabsorption of water and salt in the proximal tubules is proportional to the rate of filtration the sodium and water delivered to the distal tubules varies directly with the rate of glomerular filtration If the amount of water and salt which reaches the distal tubules is greater than the rate of distal absorption sodium is excreted while if the amount is less than the rate of distal absorption practically all the sodium will be returned to the body Since higher concentrations of sodium in serum lead to increased glomerular filtration a mechanism thereby is provided for regulating the volume as well as the concentrations of extracellular fluids The weakness of the theory lies in the fact that variations in sodium excretion have been found to occur without change in

glomerular filtration perhaps in part because the methods of measurement introduce alterations in this rate It is likely, however, that some such mechanism is involved and explains the regulation of the volume and concentrations of extracellular fluids as well as the disturbances in this regulation

The *neurohypophysis* is integrated into this system since the production of antidiuretic hormone increases when serum electrolyte concentration rises and decreases when serum electrolyte concentration diminishes The following factors have been noted to be accompanied by changes in the rate of sodium excretion fluctuations in the rate of glomerular filtration changes in the venous pressure changes in the renal blood flow alterations in the activity of the adrenal glands and the hypophysis and hypoproteinemic states The exact mechanism by which the body achieves regulation of the volume as well as the concentrations of body fluids apparently involves some combination of these factors controlling the circulation the neurohypophysis and the kidneys

Renal excretion may be divided into three phases the first of which is the formation of a filtrate With normal glomeruli the amount of filtrate is influenced chiefly by the pressure in the glomerular capillaries which in turn is controlled by the local and general factors regulating the circulation Glomerular filtration may be diminished by constriction of the renal arterioles which decreases the circulation to the kidneys This type of reaction occurs in dehydration and shock At a given extracellular volume the glomerular filtration is increased by elevation of the concentration of sodium in serum Glomerular filtration may be diminished by decrease in the number of glomeruli or by diseases of the glomeruli

Second about 85 per cent of the water and electrolyte which is filtered through the glomeruli is reabsorbed by the proximal tubules[7] The proportion of this reabsorption may vary between 60 to 90 per cent of the filtered water and electrolyte Since this operation is proportional to the rate of filtration most of the reabsorption of water sodium chloride and bicarbonate is accomplished by a process which returns a large part of the filtered water and electrolyte to the blood The evidence indicates that relatively more bicarbonate than chloride is reabsorbed at this stage of urine formation Normally practically all the glucose is reabsorbed and most of the urea remains in the urine of the proximal tubules The osmotic pressure remains the same as that

of the plasma since the proximal tubules are freely permeable to water The loop of Henle seems especially adapted to equalizing the osmotic pressure The reabsorption of water is dependent on the active transport of sodium and bicarbonate by the proximal tubules If glucose is not completely reabsorbed or if large amounts of other osmotically active substances remain less water and electrolyte are reabsorbed and more are delivered to the distal tubules

Third urine is formed from the isosmotic fluid of the proximal tubules by the distal tubular cells which reabsorb water and sodium and reabsorb or excrete other electrolytes and other substances The various operations are rather specific and at least the absorption of water and sodium can be carried out more or less independently of each other Thus the volume of water reabsorbed is influenced by the antidiuretic hormone of the hypophysis In the absence of the antidiuretic hormone large volumes of urine of low specific gravity are excreted while under the influence of this hormone the urine can be maximally concentrated by the normal kidney By an essentially separate process sodium may be reabsorbed almost completely or a large part of the sodium reaching the distal tubules may be excreted The rate of sodium reabsorption is normally regulated so as to maintain the volume and concentration of body fluids In this process the antidiuretic hormone plays an important role[3] While the necessary modifications of the rate of reabsorption of sodium may be mediated ultimately by adrenocortical hormones sodium reabsorption is increased by low concentration of sodium in plasma low filtration rates and high venous pressures It is also modified by processes regulating urinary acidity The adrenocortical hormones and to a less extent other related steroids diminish the excretion of sodium[4] If the venous pressure is raised in one kidney the tubular reabsorption of sodium is increased in this kidney but not in the other one with unaltered circulation Since the rate of glomerular filtration remains the same in both kidneys tubular reabsorption may be altered by the high venous pressure without hormonal influences or changes in the rate of glomerular filtration[70]

The regulation of the acidity of the urine provides the mechanism for excreting unusual loads of acids or alkalis In this operation hydrogen ions are exchanged for other cations by a process that is intimately connected with the rate of reabsorption of bicarbonate and carbonate[8, 9] When the serum bicarbonate is below the normal level an acid urine is excreted which contains practically no bicarbonate When the plasma bicarbonate is above 28 mEq per liter about 8 mEq

of bicarbonate are reabsorbed for each liter of glomerular filtrate While a large part of the bicarbonate reabsorption is accomplished by the proximal tubules the final regulation is carried out by the distal tubules Thus sodium and potassium are saved in acidosis, and chloride *is saved in alkalosis The reabsorption of chloride is reciprocally related* to bicarbonate reabsorption, and the sum of the two returned to the body is approximately constant for a given amount of glomerular filtrate Since the reabsorption of cations chiefly sodium, is related to the sum of chloride and bicarbonate taken back into the body the electrolyte pattern of the plasma is determined by these processes Ammonia is excreted promptly in the urine in response to an acid load but only after one to several days are large amounts of acids excreted by this mechanism During recovery from acidosis there is a delay in the decrease in ammonia formation so that there is a tendency for body sodium to become higher than normal during recovery from acidosis With the introduction of large loads of acid to be excreted sodium is at first lost from the body Later excretion of potassium diminishes the losses of sodium but may produce deficits of potassium Finally, ammonia excretion may achieve a satisfactory conservation of fixed cations[81]

The formation of an alkaline urine enables the kidneys to excrete large amounts of bicarbonate and the equivalent amounts of cations At high levels of bicarbonate the urinary pressure of carbon dioxide rises It is noteworthy that depletion of sodium and potassium as well as chloride leading to alkalosis is accompanied by excretion of an acid urine Thus the formation of an alkaline urine is not a simple response to an alkaline plasma but is modified by deficits of water and electrolyte

The regulation of body potassium by renal excretion only recently has received the attention that it deserves Potassium can be excreted by the renal tubules since the urine may contain more potassium than can be accounted for by the glomerular filtrate[8] The tubules are capable also of reabsorbing potassium against a concentration gradient since the urinary concentration may be less than that of the plasma It is probable that potassium is almost entirely reabsorbed in the proximal tubules or at least reabsorbed to the same extent as the sodium In this case the usual process is excretion by the distal tubules

Urinary potassium rises rapidly in response to increase in plasma potassium concentration Adults can excrete as much as five times the usual daily load of 4 grams When potassium intake is low urinary excretion is diminished, but some potassium is found always in the urine

The kidneys seem to have little difficulty in rendering the urinary concentration at least as low as that of the plasma Normally the rate of potassium excretion maintains the plasma concentration within narrow limits

Cellular potassium is maintained by equilibrium with the plasma potassium Under certain circumstances potassium is released from the cells to extracellular fluids and excreted Often it is difficult to decide whether the loss is dependent primarily on the release from the cells or increased excretion by the kidneys leading secondarily to cellular loss. A disturbance within the cells which releases potassium probably is in part the explanation of potassium losses in alkalosis and in response to desoxycorticosterone acetate and adrenocortical hormones Disturbances in carbohydrate metabolism in diabetic acidosis and other changes in cellular metabolism in anoxia shock dehydration and acidosis produce a similar release of potassium from the cells Urinary potassium rises so quickly in response to increase in plasma bicarbonate that the initial effect probably is chiefly renal However urinary potassium may become quite low in chronic alkalosis after considerable depletion of intracellular potassium As was indicated previously excretion of large loads of acid lead to urinary losses of potassium In part this seems to depend on factors involved in the excretion of large loads of acids However acidosis probably also releases potassium from the cells Indeed Elkinton and Winkler[3] produced evidence that potassium is released from the cells with loss of body water

The mechanism involved in the formation of an acid or alkaline urine is chiefly responsible for the preservation of the acid base balance of the blood and the body content of electrolyte In alkalosis urine chloride usually decreases owing to increase in urinary bicarbonate However it is noteworthy that acid urine is excreted in alkalosis that is accompanied by marked deficit of body electrolyte[44] The role of the relative deficits of sodium and potassium to this phenomenon has not been investigated Potassium deficit leads to increased reabsorption of bicarbonate and increased excretion of chloride since potassium deficit tends to produce chloride deficit Similarly alkalosis due to chloride deficit leads to increased potassium excretion since alkalosis tends to produce deficiency of potassium Thus not only does the kidney control body composition but renal function is determined by body composition

The abnormalities in urine formation involve so many factors that the alterations in renal function of each case may have to be analysed

individually. However, it is possible to classify the various defects of urinary excretion into the following types: (1) obligatory water excretion with little loss of electrolyte; (2) obligatory sodium excretion accompanied by proportionally smaller losses of water; and (3) excessive renal reabsorption of sodium and water. In each type disturbances in the regulation of the acid-base equilibrium may develop, and this factor must be evaluated separately.

It is obvious that if the kidneys excrete water at a greater rate than it is taken into the body, the serum electrolyte concentrations will rise unless electrolyte is excreted also. The body will contain low amounts of water and the serum will show an increase in concentration of electrolyte. The state of body water and electrolyte is hypertonic dehydration. Obligatory polyuria leading to losses of water and but little change in body sodium and chloride has been described in infants as a result of an anomaly of renal function[8]. The patients are all males; they fail to grow, have fever unexplained by infections and are mentally deficient. The diuresis fails to respond to the antidiuretic hormone. Often the loss of water becomes so rapid that the patients spend practically all their time drinking. The serums show very high concentrations of sodium and chloride without striking acidosis. The continued reabsorption of sodium and chloride in the face of rising serum concentration is the essential feature of the disease. The changes in cellular composition are not known. These patients require low intakes of sodium chloride as well as high intakes of water.

Diabetes insipidus results from deficient production of antidiuretic hormone owing to injury of the neurohypophysis.[9] The patients usually do not suffer from dehydration since they develop thirst which is gratified by drinking large amounts of water. Since the distal tubules seem to function normally with respect to reabsorption of sodium and other electrolytes, there are usually no disturbances in acid-base equilibrium or plasma electrolyte concentration. If the intake of sodium chloride is high, salt is excreted in large volumes of dilute urine. If the intake of sodium chloride is low, the kidneys save sodium chloride and excrete somewhat smaller amounts of dilute urine. The patients seem to suffer chiefly from difficulty in drinking enough water to avoid thirst produced by the obligatory urinary water losses. The symptoms of thirst and the polyuria can be overcome temporarily by injections of antidiuretic hormone or by spraying the hormone on the nasal mucous membranes[87].

Adrenal insufficiency is perhaps the purest type of obligatory excre-

tion of sodium Although the urinary excretion of sodium and chloride is accompanied by decrease in body water the concentrations of sodium and chloride in serum are low and moderate acidosis develops This indicates that the losses of sodium and chloride are relatively greater than those of water The patients suffer from hypotonic dehydration The volume of extracellular fluids is decreased while the cells have high water contents Although the primary defect in renal function is failure to conserve sodium the final picture is the result of circulatory and renal failure produced by deficit of extracellular electrolytes Sodium *deficiency is the chief explanation of the diminished circulation* the low blood pressure the low blood volume the decrease in the rate of glomerular filtration the rise in non protein nitrogen and the failure to regulate the urinary acidity These disturbances are corrected for the most part as long as body electrolytes are kept normal by the administration of suitable amounts of sodium chloride or a mixture of sodium chloride and sodium bicarbonate[3, 9] Administration of desoxy corticosterone acetate or cortical extract corrects the absorption of sodium by the renal tubules and with the restoration of body electrolyte renal function becomes essentially normal

There is evidence that potassium tends to be retained in adrenal insufficiency especially when the loss of extracellular electrolytes leads to circulatory changes and diminished glomerular filtration The muscles under these circumstances may contain excessive amounts of potassium Some evidence has been assembled that cortical hormones increase cellular water[94] If this is true the increase in intracellular water accompanying loss of extracellular electrolytes may not be as great as would be produced by a similar loss in animals with intact adrenals

Adrenal hormones are necessary for the diuresis of water since intact adrenals or cortical hormones are necessary for the development of the picture of diabetes insipidus[3] This observation is the basis of the test for adrenal insufficiency showing failure of diuresis in response to a water load[4]

A large part of the picture of Addisonian crisis is explained by deficits of extracellular electrolytes Adequate supplies of sodium chloride enable the patients to survive and perform the usual metabolic functions though the response to stress is slow and inadequate However it is clear that adrenal insufficiency involves more than disturbances due to loss of body water and electrolytes[1] Glyconeogenesis from protein and other responses to cortical hormones are not clearly associated with

the electrolyte disturbances. Nevertheless, Addisonian patients have striking adverse reactions to relatively small amounts of potassium in food, especially when there are deficits of sodium and chloride. This response has never been satisfactorily explained. Kendall has postulated that the adrenal cortex enables the body to be freed from the vicissitudes of electrolyte metabolism.[71]

Although desoxycorticosterone acetate restores renal function with respect to reabsorption of water and sodium, the compound may lead to excessive excretion of potassium. Cardiac injury may result particularly if the intake of sodium chloride is high and that of potassium low.[9] Diets should not be low in potassium or high in sodium chloride when desoxycorticosterone is administered. However, Addisonian patients do better with diets low in potassium and high in sodium chloride when no hormonal therapy is given.[96]

The excessive excretion of sodium in hyposthenuric renal insufficiency usually is accompanied by other defects in renal function. While the generalized effects of deficit of extracellular water and electrolytes may develop and aggravate the disturbances in the kidneys, this does not usually take place. The kidneys may continue to excrete sodium and chloride while the serum concentrations of these ions remain low and body water is relatively normal. The body seems to become adjusted to low concentrations of electrolytes. The urine cannot be rendered highly acid, ammonia is not adequately formed in response to acidosis, phosphate and sulphate are poorly excreted, and the urinary concentrations remain constant and low. Since the usual diet requires the excretion of an acid urine in order to preserve body electrolytes, acidosis results. Some cases of chronic renal insufficiency have shown flaccid paralysis accompanied by low serum concentrations of potassium and responding to administration of potassium.[3] The kidneys of these patients apparently are unable to conserve potassium. It is likely that diets high in sodium chloride aggravate this tendency. Some patients with chronic nephritis develop acidosis associated with deficits of both sodium and potassium. The decrease in extracellular sodium is explained in part by the transfer of sodium to the cells owing to deficit of potassium, since analyses of the muscles have shown low potassium and high intracellular sodium.[33]

In the terminal stages of nephritis, particularly when oliguria has developed, the excretion of potassium is diminished, serum potassium concentration rises, and death may result from potassium intoxication.[31, 3] Along with the elevation of serum potassium a few pa-

tients have shown a flaccid paralysis and weakness with electrocardiographic changes characteristic of high serum potassium and relief of the symptoms when the administration of saline solutions has reduced the serum potassium concentration[3]

If the patients have circulatory disturbances as the results of decrease in the volume or concentrations of extracellular fluids improvement follows administration of water and sodium chloride Renal function also may be improved in some cases with low serum electrolyte if sufficient sodium chloride and sodium bicarbonate are administered to replace the urinary losses despite little effect on the circulation This effect seems to depend on increase in the urine volume It is difficult to *achieve stable normal concentrations of electrolyte in the serum of* many cases of nephritis If excessive amounts of salt are given serum electrolyte concentrations may become abnormally high or edema may be produced or aggravated Relief from acidosis follows the administration of sodium bicarbonate but the effect seldom is prolonged If large amounts of sodium bicarbonate are given to patients with chronic nephritis a highly alkaline urine is not formed and alkalosis is produced

There is evidence that administration of large amounts of sodium bicarbonate in the therapy of peptic ulcer produces renal insufficiency as well as profound alkalosis[8, 94] The patients lose their appetites and develop lassitude weakness headache nausea and vomiting Mild stupor coma or psychic disturbances occur The non protein nitrogen rises and returns to normal slowly only after the serum electrolyte concentrations are restored In some cases the alkalosis seems to have produced permanent renal damage It is not certain however that alkalosis permanently injures the normal kidney but there is little doubt that it aggravates the pathological process in the kidney already abnormal[79]

Disturbances leading to excessive reabsorption of water and electrolytes tend to produce edema As was previously indicated the function of the distal tubules which provide the mechanism for the reabsorption of water and electrolyte is the one that is ultimately responsible for regulating the volume and concentrations of body fluids Particularly in this operation the kidneys are under the influence of the factors controlling the circulation the neurohypophysis and the endocrines It is not surprising therefore that disturbances in the reabsorption of water and electrolyte by the kidney may arise primarily from generalized circulatory diseases and even when the kidneys are primarily involved disturbances involving control of the circulation develop The circula

tory disturbances aggravate the difficulty of renal origin and changes in the kidneys develop in primary circulatory disorders

The edema of cardiac failure arises chiefly from circulatory factors leading to increased reabsorption of sodium and water in the distal tubules[10] Nevertheless venous stasis augments the capillary pressure and explains some of the accumulation of fluid, low concentrations of albumin in serum may develop and have a similar effect It is not known whether the tubular absorption is increased owing to high venous pressure in the kidneys to decrease in the rate of glomerular filtration to hormonal influences or to a combination of these factors In any case there is no permanent renal damage since the kidneys respond normally when the circulation is improved Other types of circulatory failure probably lead to disturbances in renal circulation which involve retention of water and electrolyte Decrease in the effective plasma volume is an important factor leading to increased reabsorption of sodium and water by the kidneys since the following conditions are associated with this phenomenon hypoproteinemic states with or without renal disease hemorrhage shock dehydration exercise assumption of the posture and certain liver diseases

The effect of mercurial and certain other diuretics has been thought to depend on decrease in the reabsorption of sodium in the distal tubules William Wallace and associates have unpublished data which throw light on certain features of the diuresis In many patients chloride is lost in excess of sodium so that alkalosis develops When this occurs mercurial diuretics are likely not to produce further loss of body fluids Other patients lose sodium and chloride in the proportions found in extracellular fluids and are likely to show continuous diuretic response Restoration of chloride concentration by ammonium chloride usually restores the diuretic response in the patients developing alkalosis Although some of the patients developing alkalosis lose body potassium the losses are not great and they do not develop in all cases Apparently the mercurial diuretics produce a disturbance in renal function leading to relative chloride deficits with a minimal tendency to potassium loss In this type of alkalosis potassium chloride is hardly indicated since the diet contains abundant potassium and deficit of chloride is the chief cause of the alkalosis

Edema is a prominent feature of a number of different types of renal diseases such as acute hemorrhagic nephritis, nephrosis and some types of chronic nephritis In acute hemorrhagic nephritis increase in the permeability of the capillaries to proteins plays a role in the develop

ment of edema In other types of renal diseases cardiac failure occurs In most types of marked edema regarded as primarily nephrogenic low concentration of serum albumin develops It is a frequent observation that diuresis occurs without restoration of the concentration of serum albumin Nevertheless diuresis may be quite regularly induced by the repeated injection of purified plasma albumin While this procedure usually raises the serum albumin concentration it has not been proved that the diuretic effect is merely a result of mobilizing water and electrolytes from the interstitial fluids The diuresis may be a response of the tubular cells to the increase in plasma volume and other factors involving the general circulation

Coller and associates[101, 102] point out that for one to three days after major operations the kidneys fail to excrete sodium chloride in normal amounts if salt is given and fail to have a water diuresis in response to a load of intravenous glucose solution After operations the urine volume is low Administration of salt solution alone may produce high serum electrolyte concentrations or edema Injections of large amounts of glucose solution may reduce serum electrolyte concentrations Unless there is shock which leads to obligatory expansion of interstitial fluids or there are deficits of extracellular water and electrolytes postoperative patients need but small amounts of water and electrolyte Every effort should be made to prevent shock during operations by transfusion which *replaces the* blood losses but if shock develops additional transfusions should be given[103] Since deficit of extracellular electrolytes increases the susceptibility to shock water and electrolyte deficits must be replaced before operations as well as after operations if electrolyte losses are occurring

Van Slyke[104] has discussed the disturbances in renal function resulting from shock The immediate effect is oliguria or anuria With decrease in the effective circulating volume peripheral vascular constriction may restore urine flow if the blood volume is not too low If the shock is severe the kidney may be included in the peripheral vascular constriction and oliguria may result despite the maintenance of a blood pressure as high as 100 mm of mercury If renal blood flow does not remain low too long restoration of blood volume will be followed by rapid recovery However prolonged anoxia may produce renal damage which is particularly prominent in the loop of Henle and the distal renal tubules These tubules seem to become indifferent to water and electrolytes and anuria results from the reabsorption of practically all the glomerular filtrate Anuria and marked oliguria following shock

may lead to death in 2 to 20 days Although the lesions may produce anuria or marked oliguria for several days regeneration and recovery often occur In many cases the recovery will leave permanent renal damage which still is compatible with life[10]

The treatment of renal disturbances accompanying shock should shorten the period of renal anoxia by prompt transfusions of blood and replacement of deficits of water and electrolyte if they are present When the oliguria is prolonged recovery is most likely if body water and the concentrations of electrolyte in body fluids are kept as nearly normal as possible[106] This end can be attained by initial administration of appropriate amounts of water sodium chloride and sodium bicarbonate to restore body fluids Blood volume may have to be sustained by transfusions During prolonged oliguria sufficient water must be supplied from day to day to replace the obligatory expenditure which will be low owing to failure of urine formation One must avoid giving enough water to decrease the concentration of plasma electrolyte or enough sodium chloride to expand greatly extracellular fluids The therapeutic program should be controlled so that body weight remains relatively constant while enough water and electrolyte are given to keep electrolyte concentrations normal as determined by frequent analyses of the serum High water intakes will not increase urinary volumes in this type of intrinsic renal damage Furthermore low serum electrolyte concentrations may produce general circulatory disturbances which interfere with renal recovery The opinion that water is effective in oliguria arises from the fact that one kind of oliguria is produced by deficits of water and electrolytes and is treated effectively by replacing the deficits The fluids may be given by mouth if there is no nausea or vomiting but intravenous therapy usually is necessary in severe cases Diets may be given if they do not induce vomiting or nausea They should contain practically no protein or potassium Sufficient glucose or carbohydrate should be given each day to provide *maximal protein sparing* *This will decrease the rate of release of potas*sium from the katabolism of tissues Since proteins and amino acids accelerate the final toxic reaction they are contraindicated

During convalescence from oliguria the urine is likely to be low in concentration In some cases sodium will be poorly reabsorbed but after some disturbances recovery of sodium reabsorption may occur while failure of reabsorption of water persists[106, 107] Since some of these patients have had cerebral symptoms it is possible that there is injury to the neurohypophysis which leads to deficient production of the

antidiuretic hormone At least in some of these patients increased serum electrolyte concentration has occurred on normal salt intakes Some patients with calcification of the renal tubules show hyposthenuria with high concentrations of sodium and chloride in the serum[1, 3, 14] Treatment must consider these possibilities

Therapy of renal disturbances is based on the calculation of the rate of water and electrolyte expenditure and the changes in body composition that the losses of water and electrolytes have produced Determinations of the serum electrolyte concentrations usually are necessary but these do not accurately reveal the intracellular changes When the urinary specific gravity is fixed at 1 012 about 85 ml of water is required to excrete the load created by metabolizing 100 calories This indicates that the water intake may have to be as high as 150 ml per 100 calories metabolized The load may be reduced by diets low in protein but protein should not be lower than that which will support good nutrition As was indicated salt may have to be added if it is wasted but in consideration of the effect of high intakes of sodium on the blood pressure and the formation of edema salt is given with caution

Finally in considering the factors controlling the expenditure of water and electrolyte it is necessary to point out that the shifts of water and electrolyte within the body change the amount that is available for expenditure If there is increase in extracellular fluids owing to the formation of edema or exudates sufficient water and electrolyte must be retained to maintain the concentrations of extracellular fluids When such fluids are excreted a corresponding amount of water and electrolyte is released These facts must be borne in mind in estimating the requirement of water and electrolyte

There is such a small amount of water and electrolyte in the body that can be safely used for the obligatory expenditure that small losses produce symptoms of dehydration The dangers of dehydration have been sufficiently emphasized so that physicians do not knowingly call on body water to cover obligatory expenditure It is not so generally realized that expansion of body fluids may leave the rest of the body with insufficient water and electrolyte for the renal and circulatory systems to function properly Burns exposure to cold extensive trauma inflammatory reactions and injury due to ischaemia produce large expansions of fluids at the site of the injury The fluid accumulated resembles extracellular fluids and the localization of the water and electrolyte has the same effect as loss of extracellular water and electrolyte[3]

Accompanying the circulatory changes of tissue injury, potassium may be released from the cells and replaced by sodium[40]. The decrease in extracellular sodium produces acidosis which is further aggravated by changes in renal function dependent on the lack of water and electrolyte for the renal and circulatory systems. Part of the benefit of salt therapy in shock is dependent on these changes in the cells and the obligatory expansion of extracellular fluids.

Specific ion effects from the changes in concentration of sodium and chloride are not recognized except that alkalosis may produce or aggravate tetany. However, certain disturbances develop which are attributed to low or high concentrations of potassium in plasma.

Hypokaliemia

The following signs and symptoms have been observed when the serum potassium concentrations are low: (1) weakness and hypotonia of the skeletal muscles progressing to frank paralysis; (2) dyspnea with a gasping type of respirations in which the accessory muscles of respiration are involved; (3) cyanosis which usually is respiratory but may be cardiac; (4) abdominal distention which probably is dependent on atonia of the smooth muscle; in experimental animals and probably in patients extreme deficiency of potassium may produce paralytic ileus; (5) nausea and vomiting; (6) cardiac enlargement with the appearance of systolic murmurs; (7) increased pulse pressure with Corrigan pulse; (8) elevated venous pressure and signs of cardiac failure. The paralysis of the diaphragm and the abdominal muscles and the functional disturbances in the myocardium account for the major clinical signs and symptoms. The electrocardiographic changes are described later.

Physiologically significant decrease in the concentration of potassium in serum may occur without characteristic signs and symptoms. Nevertheless, most of the symptoms just mentioned occur chiefly when the serum concentration is low. However, while the serum concentration is likely to be low when there is deficiency of potassium in the cells if there is abundant water available and the circulation is adequate, large deficiencies in the cells occur when the circulation is poor and the serum concentrations of potassium are normal or high. For this reason the specific signs and low serum potassium concentrations will enable the physician to recognize only a minority of the cases of potassium deficiency.

Hyperkalemia

The following signs and symptoms have been recognized in hyperkalemia (1) listlessness and mental confusion (2) numbness and tingling of the hands and feet with a sense of weakness and heaviness of the legs (3) cold gray pallor (4) bradycardia and occasionally totally irregular rhythm (5) peripheral vascular collapse with diminished heart sounds and low blood pressure (6) in a few uremic patients a rapidly ascending flaccid paralysis with less involvement of the trunk head and bladder than the arms and legs and (7) cardiac arrest

Electrocardiograms in Hypo and Hyper Kalemia

There are progressive changes in the electrogram which correlate roughly with the concentration of potassium in the serum These are illustrated diagrammatically in chart VII When the concentration of potassium is low (below 3 mM per liter) the following alterations have been noticed (1) slightly prolonged QT interval (2) decrease in the height and inversion of the T waves (3) rounded and prolonged T waves which may run into the P waves (4) depression of the ST segment and (5) possibly inversion of the P waves extrasystoles and AV block The precordial lead CR3 has been the most useful in measuring the QT interval The height of the T waves has been found to be influenced by the pH partial carbon dioxide pressure and the concentration of potassium The changes in the electrocardiogram are reversed by restoration of the concentration of potassium in serum when low concentration of this ion is the cause of the change[11, 12, 13]

The changes in the electrocardiogram accompanying elevation of the concentration of potassium in serum are fairly characteristic The T waves may become elevated and peaked at concentration of potassium in serum as low as 6 5 to 7 8 mM per liter These changes are present invariably at concentrations greater than 8 mM per liter Increase in the duration of the QRS complex develops after the change in the T waves Increased duration of the PR interval leading to auricular standstill then develops Totally irregular rhythm and heart block develop at concentrations of 10 mM per liter or slightly more[1]

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respect to the limitations imposed by the metabolic disturbances of the particular disease Only the general principles will be outlined in the following paragraphs The aim of fluid therapy is the restoration and maintenance of normal composition of the body particularly with respect to water and electrolytes

When there is no nausea and vomiting and when oral fluids do not seriously aggravate the losses of fluid from the gastrointestinal tract the oral administration of fluid or food is the method of choice If one is attempting to restore electrolyte by mouth the concentrations of the fluids given seldom should be greater than one third physiological strength Concentrated salt solutions are likely to produce nausea vomiting or diarrhea and do not supply enough water without electrolyte to cover the obligatory expenditure as insensible water and as water required for urine formation The various required ions may be added to beverages or food The usual intake of potassium for an adult on a full diet is 4 grams of potassium or the equivalent of about 8 grams of KCl This amount may be safely given orally and usually suffices to replace deficits of this ion However more may be given since it is difficult to induce potassium intoxication by potassium taken orally except when renal excretion is limited owing to adrenal insufficiency renal disease or circulatory failure Children and babies may be given corresponding amounts but dosage should be based on the relative caloric production rather than the relative weight The usual diets provide enough electrolyte unless there are large deficits or unusual losses

Parenteral therapy is required when large deficits must be replaced or fluid cannot be taken orally Electrolyte solutions containing chiefly sodium at physiological concentrations are well tolerated subcutaneously For slow intravenous injection the fluids may be about three time physiological strength However solutions more concentrated than physiological saline should not be used except when it is desirable to raise the serum concentrations As the sole source of water physiological saline and other similar solutions do not provide enough water free of electrolyte When all fluids are given parenterally the electrolyte concentration in the mixture given over 24 hours should seldom be greater than one third physiological saline Usually the total requirement of water and electrolytes for twenty four hours is estimated and added to 5 or 10 per cent solution of glucose Such a mixture may be injected slowly into a vein If the solution is injected slowly and the

SUMMARY

The purpose of this chapter is to present the physiological basis for fluid therapy. The chief factors to be considered are (1) the changes

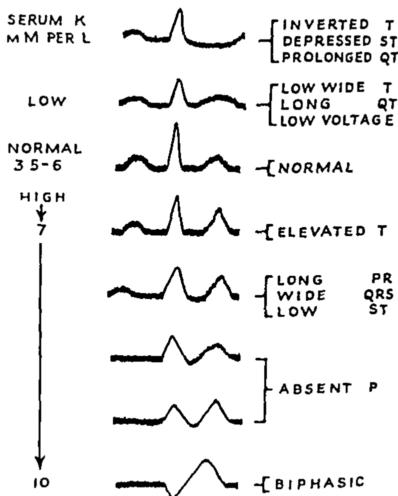


CHART VII Diagrams of electrocardiogram with changing concentration of serum potassium

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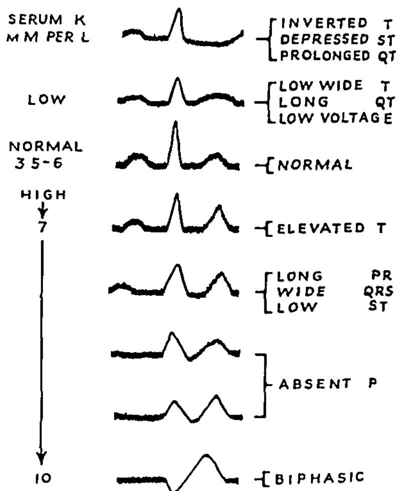


Chart VII Diagrams of electrocardiogram with changing concentration of serum potassium

in tissue composition and (2) the rate of expenditure of water and electrolytes The knowledge of these factors must be applied with due

lent has few of these objections Molar sodium lactate should be diluted to one seventh molar if injected subcutaneously or to less than one third molar if injected intravenously The solutions containing potassium that are designed for subcutaneous administration (Darrow s solution or the mixture of NaCl and KCl) should be diluted one part to or 3 parts of 5 or 10 per cent glucose if injected intravenously While solutions of amino acids or proteins hydrolysates have been injected subcutaneously in a 3 per cent solution they are irritating locally

The table shows the analysis of one type of enzyme hydrolysate of caseine and these values do not apply to other preparations Solutions are available that contain practically no sodium and potassium If the electrolyte content is critical the analysis of the particular solution used should be consulted Only the electrolyte content of the plasma was estimated in the case of whole blood since the electrolyte of the cells is not immediately available to the body as a whole

TABLE II

SUITABLE MAINTENANCE REQUIREMENTS PER 100 CALORIES METABOLIZED

	H O	*Protein Amino Acids*	*Glucose*	*NaCl*	*KCl*
Gm	90–150	[illegible]	22	0 06–0 1	0 0 –0 14
mM				1	

Table II shows the estimated requirements when all fluids must be administered parenterally and when there are no abnormal losses and no unusual amount of sweat Under these circumstances the expenditure of sodium potassium and chloride is small and the fluids administered should not contain more than about 10 ml of physiological saline Twenty ml per 100 calories metabolized of a mixture of equal parts physiological saline and isotonic potassium chloride (4 5 gm NaCl and 5 5 gm KCl per liter) meets the expenditure of Na K and Cl It will be seen that the caloric requirement cannot be supplied except by injecting about 150 ml of 15 per cent glucose or 220 ml of 10 per cent solution A fifteen per cent solution is irritating to the veins and may produce thrombosis Two hundred and twenty ml per 100 calories is a high fluid intake and while it may be used it is seldom desirable Fortunately it is seldom necessary to prescribe full calories since the consumption of a moderate amount of tissue fat is of little moment except that it delays the recovery of body protein The use of homog

amount of glucose does not provide more calories than are being burned there is little glycosuria

Certain useful solutions for parenteral therapy are listed in Table I. They are classified according to the chief metabolic need which they meet. The preferred method of administration is indicated by + while

TABLE I

Selected List of Fluids Used in Parenteral Fluid Therapy

	Contents per Liter							Daily Dose		
	Cl mM	Na mM	K mM	L mM	Glucose gm	Intravenous	Subcutaneous	per kgm cc	per 100 cal met cc	Chief Use
Appropriate for Water Expenditure										
Glucose	0	0	0	0	50	+	(+)		80 120	Nutrition
Glucose	0	0	0	0	100	+			80 120	Nutrition
Appropriate for Na and Cl replacement										
Saline	154	154	0	0	0	+	+	20-80		Alkalosis
1/7 M Na Lactate	0	143	0	0	0	+	+	20 60		Acidosis
Na Lactate Na Cl	101	148	0	0	0	+	+	0 80		Acidosis
M Na Lactate	0	1000	0	0	0	(+)		4 8		Acidosis
3 75% $NaHCO_3$	0	45	0	0	0	+				Acidosis
Appropriate for Na Cl and K replacement										
Darrow	104	1 0	36	0	0	(+)	+	20 80		Acidosis
Butler Talbot	2	30	15	5	50	+			100 150	Acidosis
Butler Talbot	2	30	15	5	100	+			100 150	Acidosis
NaCl KCl	137	10	36	0	0	(+)	+	20 80		Alkalosis
Appropriate for Parenteral Feeding										
Hydrolysate of Caseine	33	50	7	9	50	+	(+)		5 50	Nutrition
Appropriate for Shock										
Whole Blood	32	80	4			+		5 30		Shock
Plasma	80	00	10			+		5 40		Shock

All solutions are used to replace water and provide for expenditure according to the categories indicated in the table

(+) indicates that the solution should be modified by dilution or that there are serious drawbacks to this method of administration. The subcutaneous injection of 5 per cent solution of glucose is irritating locally and immobilizes water and electrolyte for several hours. A mixture of one part 5 per cent glucose and one part physiological saline or equiva

rapidly The authors believe that the optimal dose that is safe and efficiently utilized is 3 mM of potassium (0 gms of KCl) per kilogram per day One to two mEq of potassium per kilogram per day usually is sufficient to produce potassium retention and prevent serious decrease in serum potassium concentration The injection of the dose for one day should be at a rate that requires 4 hours or more for the total amount since this assures that there is time for equal distribution of potassium throughout body fluids When there is oliguria owing to shock or dehydration the concentration of potassium in serum may be high In order to minimize the dangers of potassium intoxication intravenous injection of about 0 ml per kilogram of a solution containing sodium chloride or sodium chloride and sodium lactate at physiological strength should precede the use of solutions containing potassium This will improve the circulation and start renal excretion so that it is safe to inject the solution containing potassium This procedure need not delay starting the potassium therapy by more than an hour In cases with high electrolyte concentrations in serum it is advisable to use a salt mixture diluted about half with 5 per cent glucose or only 5 per cent glucose It usually takes 4 to 6 days to replace a large deficit of potassium

In alkalosis physiological saline is effective unless there are large deficits of potassium Theoretically the mixture of sodium and potassium chloride is more appropriate in most cases and has been proved to be more effective in cases of alkalosis resulting from prolonged vomiting or as a result of post operative suction

The treatment of marked oliguria and anuria as a result of intrinsic renal disease was discussed briefly in connection with shock Coller and associates have pointed out that for 1 to 3 days after operations the kidneys fail to respond to certain renal loads that have been a part of post operative care in many hospitals The kidneys fail to excrete sodium and water adequately For this reason the water and electrolyte expenditure of post operative patients is temporarily low and the fluids prescribed should be correspondingly reduced However if there is shock or if deficits of water and electrolyte develop the intake of salt solutions should be higher The best method of treating post operative shock is by transfusions preferably by giving blood at the time of operations according to the blood losses Since patients with deficits of water and electrolyte do not withstand operations well such deficiencies always should be replaced before operations

emized suspensions of fat is being carried out successfully but still is experimental If the use of intravenous fat becomes generally available complete parenteral feeding will be theoretically possible It is usually advisable to add one of the intravenous preparations of vitamins when prolonged parenteral therapy is being carried out

In most examples of severe dehydration, shock is likely to develop The circulatory failure accompanying loss of extracellular water and electrolytes is treated most effectively by replacing these deficits, but transfusions of blood and to a lesser extent, plasma improve the results When potassium solutions are going to be given to patients suffering from severe dehydration or shock, it is important to start the treatment with the intravenous injection of 10 to 20 ml of saline or a mixture of sodium chloride and sodium lactate This procedure is indicated because the concentration of potassium in serum is likely to be slightly high despite a large intracellular deficit of potassium Salt solutions will improve the circulation and renal function so as to minimize the dangers of potassium intoxication However it is seldom necessary to delay the injection of the solution containing potassium more than an hour Since the potassium containing solution is injected slowly, the rate can be diminished if renal function remains impaired

In the authors experience it is seldom necessary in severe acidosis due to infantile diarrhea to give more sodium bicarbonate or lactate than is contained in Darrow s solution Since this condition is accompanied by as great losses of electrolyte as are met in any other conditions this solution should be equally effective in other types of severe acidosis due to electrolyte depletion If it seems necessary to give sodium bicarbonate or lactate, the dose is indicated in the table It should be remembered that acidosis usually is accompanied by deficits of potassium as well as sodium and that the administration of potassium makes it unnecessary to give large doses of sodium bicarbonate to restore the serum concentrations of bicarbonate

The deficits of extracellular electrolyte are unlikely to be greater than one third of the normal extracellular contents or 9 mM of chloride or 12 mM of sodium per kilogram of body weight The deficit of these ions may be replaced rapidly by intravenous or subcutaneous injections The deficit of potassium is unlikely to be greater than 17 mM per kilogram of body weight This deficit cannot be restored rapidly because the injection of potassium at a rapid rate and in too large amounts may produce potassium intoxication Furthermore the cells do not seem to be able to repair the deficiency of intracellular potassium very

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